

## Insights into brain architectures from the homological scaffolds of functional connectivity networks

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Provisional

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# Insights into brain architectures from the homological scaffolds of functional connectivity networks

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## 2 ABSTRACT

3 In recent years, the application of network analysis to neuroimaging data has provided useful  
4 insights about the brain's functional and structural organization in both health and disease. This  
5 has proven a significant paradigm shift from the study of individual brain regions in isolation.  
6 Graph-based models of the brain consist of vertices, which represent distinct brain areas,  
7 and edges which encode the presence (or absence) of a structural or functional relationship  
8 between each pair of vertices. By definition, any graph metric will be defined upon this dyadic  
9 representation of the brain activity. It is however unclear to what extent these dyadic relationships  
10 can capture the brain's complex functional architecture and the encoding of information in  
11 distributed networks. Moreover, because network representations of global brain activity are  
12 derived from measures that have a continuous response (i.e. interregional BOLD signals), it is  
13 methodologically complex to characterize the architecture of functional networks using traditional  
14 graph-based approaches. In the present study, we investigate the relationship between standard  
15 network metrics computed from dyadic interactions in a functional network, and a metric defined  
16 on the *persistence homological scaffold* of the network, which is a summary of the persistent  
17 homology structure of resting-state fMRI data. The persistence homological scaffold is a summary  
18 network that differs in important ways from the standard network representations of functional  
19 neuroimaging data: i) it is constructed using the information from all edge weights comprised  
20 in the original network without applying an *ad hoc* threshold and ii) as a summary of persistent  
21 homology, it considers the contributions of simplicial structures to the network organization rather  
22 than dyadic edge-vertices interactions. We investigated the information domain captured by the

23 persistence homological scaffold by computing the strength of each node in the scaffold and  
24 comparing it to local graph metrics traditionally employed in neuroimaging studies. We conclude  
25 that the persistence scaffold enables the identification of network elements that may support the  
26 functional integration of information across distributed brain networks.

27

28 **Keywords:** functional connectivity, fMRI, persistent homology, homological scaffold, integration & segregation

## 1 INTRODUCTION

29 The application of graph theoretical analysis to neuroimaging data has provided important new insights  
30 about the functional organization of the human brain in health and disease. Graph measures considering  
31 the global properties of brain networks have notably helped shape our understanding of the system-wide  
32 functional architectures which enable the brain to balance the segregation and integration of information  
33 in macro-scale networks [6, 7]. Complementary to these system-wide characteristics, local graph metrics  
34 have been used to quantify the relative importance of individual brain areas towards routing information in  
35 brain networks according to different criteria (section 2.3).

36 Whilst standard graph metrics are powerful descriptive means to characterize functional neuroimaging  
37 data at the whole-brain scale, they also involve significant conceptual and methodological limitations.  
38 First, these measures are exclusively based on *dyadic* (i.e. pairwise) interactions between edges and  
39 vertices. In practice, this means that the basic "unit" of the graph is an edge connecting a pair of nodes. By  
40 contrast, it is well established that neural computations performed by distributed ensembles of brain regions  
41 underlie higher cognitive phenomena and even resting-state dynamics in the human brain. As described  
42 in detail below, methods from *algebraic topology* provide an alternative for encoding such non-dyadic  
43 relationships. Specifically, the concept of *simplicial complexes* allows one to describe relations between  
44 distributed subpopulations of network elements without sacrificing access to many of the fundamental tools  
45 of network science [19].

46 Secondly, the adjacency matrices which form the basis for constructing network representations are  
47 derived from measures that have a continuous response and are therefore typically weighted, fully connected,  
48 and signed. That is, the value of the pair-wise measure of association (i.e. bivariate/partial correlation,  
49 phase synchrony, transfer entropy, mutual information) between the activity signals across brain areas  
50 is non-zero, varies considerably across region pairs, and may include both positive and negative values.  
51 Therefore, *ad hoc* thresholding methods are commonly employed in functional neuroimaging studies to  
52 selectively prune connections within the graph leading to sparser, binary network representations with  
53 more naturally interpretable attributes. An exhaustive discussion of the methods used for thresholding  
54 brain networks is beyond the scope of this study. It should however be noted that a majority of these  
55 strategies lead to the elimination of *weak and/or negative* connections within a network. Yet, it has been  
56 demonstrated that standard graph measures are unstable across the threshold ranges typically employed in  
57 functional connectivity studies [18] and very few neuroimaging analysis methods actually account for the  
58 statistical significance of individual connections [24, 23, 30]. Thus, while neglecting weak links enhances  
59 information clarity, it may well do so at the expense of information completeness. Previous studies have  
60 indeed shown weak links to significantly contribute to brain functional processes including: resting-state  
61 networks, disease states, and cognition [36, 2, 11, 35]. Furthermore, synchronous neural oscillations can be  
62 maintained even with very weak synaptic links [8] and complex systems research has provided considerable

63 evidence for the contributions of weak links to the stability of large networks in a range of social and  
64 biological systems [20, 12, 29, 28, 27].

65 An alternative to traditional network analysis methods is the use of the *homological scaffolds* of the  
66 weighted network [31] to summarise information about the persistent homology of the data. Persistent  
67 homology is a recent technique in computational topology [44, 10, 26] that will be described in detail in  
68 section 2.2. In summary, homology characterizes a topological space by counting its holes of different  
69 dimensions (see 2.2.2 for definitions). Persistent homology characterises the importance and stability  
70 of the holes in the original data through a process called filtration. It is accordingly a specific type of  
71 *mesoscopic organization* of the vertices and edges and their respective importance that is considered in the  
72 persistent homology analysis. This enables one to explore the network's organization from a non-dyadic  
73 perspective, consistent with the brain's large-scale ensemble coding mechanisms. Holes are the mesoscopic  
74 (anti-)structures remaining in the topological space that are not bounding a higher dimensional simplex.  
75 The case of 1-dimensional holes, or "cycles", to which we restrict ourselves in this study, is intuitive to  
76 visualise (Fig. 1): a cycle is a closed loop of length greater than three.

77 The network organization of the human brain is characterized by a large number of distributed network  
78 modules which perform segregated local computations [33, 38]. There has recently been much interest  
79 towards identifying the "hub" regions which enable global communication across segregated brain modules,  
80 and the integration of these local computations over space and time [21]. The homological scaffolds  
81 summarises the role of network edges constituting the cycles during the filtration process; enabling to  
82 identify edges belonging to multiple cycles and/or highly persistent cycles along the filtration. A hypothesis  
83 tested in this study is that the edges supporting these mesoscopic network anti-structures will be well  
84 positioned to bridge together segregated functional brain modules, rather than participate in densely  
85 connected local networks.

86 The present study investigates the relationship between standard network metrics computed from dyadic  
87 interactions in a functional brain network, and metric computed on the *persistence homological scaffold*  
88 of the network. Toward this aim we generate a persistence scaffold from the whole-brain functional  
89 connectivity data of healthy subjects recorded during resting-state fMRI. We then convert edge-persistence  
90 scaffold values into a node-level measure termed *persistence scaffold strength (PSS)* which enables  
91 comparisons between the persistence scaffold and local graph metrics computed on the original network.  
92 We introduce this new measure because homological scaffold theory does not yet include node-level metrics  
93 analogous to the topological centrality measures typically used in the analysis of functional brain networks.  
94 We find that the unique mathematical attributes of the persistence homological scaffold may render it useful  
95 for identifying key local nodes supporting the global integration of information processing directly from  
96 functional neuroimaging data.

## 2 MATERIAL & METHODS

### 97 2.1 Data

#### 98 2.1.1 Study Participants

99 Neuroimaging data were collected at CFIN, Aarhus University Hospital, Denmark, from 16 healthy right-  
100 handed participants (11 men and 5 women, mean age:  $24.7 \pm 2.5$ ). Participants with a history of psychiatric  
101 or neurological disorders were excluded from participation in the study. The study was previously approved  
102 by the Center of Functionally Integrative Neuroscience internal research board. The study was performed

103 in accordance with the Declaration of Helsinki ethical principles for medical research and ethics approval  
104 was granted by the Research Ethics Committee of the Central Denmark Region (De Videnskabsetiske  
105 Komiter for Region Midtjylland). Informed consent was obtained from all participants.

### 106 2.1.2 MRI data acquisition

107 MRI data were collected in one session on a 3T Siemens Skyra scanner. The parameters for the structural  
108 MRI T1 scan were as follows: voxel size of  $1\text{ mm}^3$ ; reconstructed matrix size  $256 \times 256$ ; echo time (TE) of  
109 3.8 ms and repetition time (TR) of 2300 ms. The resting-state fMRI data were collected using whole-brain  
110 echo planar images (EPI) with TR = 3030 ms, TE = 27 ms, flip angle =  $90^\circ$ , reconstructed matrix size =  
111  $96 \times 96$ , voxel size  $2 \times 2\text{ mm}$  with slice thickness of 2.6 mm and a bandwidth of 1795 Hz/Px. Seven minutes  
112 of resting state fMRI data were acquired for each subject.

### 113 2.1.3 MRI data processing

114 We used the automated anatomical labeling (AAL) template [40] to parcellate the entire brain into  
115 90 cortical and subcortical regions (45 for each hemisphere) which represented the nodes in functional  
116 connectivity networks. The parcellation was conducted in the EPI native space. Linear registration was  
117 performed using the FSL toolbox ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl), FMRIB, Oxford) [37]. The EPI image was  
118 co-registered to the T1-weighted structural image, and the T1-weighted image was coregistered to the T1  
119 template of ICBM152 in MNI space. The resulting transformations were concatenated and inversed and  
120 further applied to warp the AAL template from MNI space to the EPI native space, where interpolation  
121 using nearest-neighbor method ensured that the discrete labelling values were preserved. Initial fMRI data  
122 preprocessing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL and  
123 consisted of: motion correction using MCFLIRT; non-brain tissue removal using BET; spatial smoothing  
124 using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by  
125 a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line  
126 fitting, with  $\sigma = 50.0\text{s}$ ).

### 127 2.1.4 Functional Connectivity Analysis

128 We used FSL to extract and average the time courses from all voxels within each AAL cluster. We then  
129 used Matlab (The MathWorks Inc.) to compute the pairwise Pearson correlation between all 90 regions.  
130  $R$ -values were transformed to  $z$ -values via Fisher transformation, and the resulting  $z$ -values composed the  
131 final  $90 \times 90$  functional connectivity (FC) matrix. We averaged the FC matrices for all 16 participants to  
132 obtain a group-averaged  $90 \times 90$  FC matrix.

## 133 2.2 Persistent homology and scaffolds

134 The next two sections will introduce fundamental notions needed to understand persistent homology,  
135 which is presented in the third section. Homological scaffolds are then defined and a toy example is  
136 presented in the penultimate section. The last section exposes the open problem and implications of  
137 the choice of a cycle's representative in the filtration. The workflow is illustrated in Fig. 2 and can be  
138 summarised as follows: one starts from the data, that for the sake of generality we will assume to be a fully  
139 connected, weighted and signed matrix. As the matrix is square and symmetrical, one can interpret it as an  
140 undirected network adjacency matrix. The persistent homological features of the data are then computed  
141 and finally summarised in the persistence and frequency scaffolds. These scaffolds can be seen as an edge  
142 centrality measure, that emphasizes the role of an edge in the persistent homological characterisation of the  
143 original data but they can also be considered as network in itself and analysed as such, as we define the

144 *PSS* in section 2.3.3. For a comprehensive introduction to persistent homology, the interested reader is  
145 invited to consult [44, 10, 26].

146

## 147 2.2.1 Simplices, Simplicial Complex, and Holes

148 A *simplicial complex* can be seen as a generalisation of a graph, where interactions, instead of being  
149 strictly between nodes, are between objects called *simplices* that generalise the notion of nodes. In the  
150 present context, a node is a 0-dimensional simplex, an edge a 1-dimensional simplex, (representing a binary  
151 interaction) a full triangle is a 2-dimensional simplex (representing ternary interactions), and so on for  
152 higher dimensions. A *simplicial complex* is thus a type of topological space that is a collection of simplices  
153 of any dimension (Fig.1).

154 There are many types of simplicial complexes. In this study, we focus on *clique complexes*, which can  
155 be constructed from any network. In graph theory, a *clique* is a subset of vertices of a graph in which  
156 every pair of vertices is adjacent. Thus a  $k$ -clique is a completely connected subgraph  $K_k \subset G$ , composed  
157 by  $k$  nodes containing all the possible edges among its nodes. When representing a simplicial complex,  
158 simplices are typically shaded, or filled in to identify them (Fig. 1). Importantly, upon identifying all the  
159 simplices in a clique complex, structures called *holes* can remain, and these are the structures of interest  
160 in this analysis (Fig.1). A hole of dimension  $k$ , or  $k$ -hole, is a hole bounded by simplices of dimension  $k$ .  
161 In this paper, we focus on holes bounded by 1-dimensional boundaries, also called "cycles". In a clique  
162 complex, a cycle is a minimal closed path of length greater than 3 (Fig. 1). This is due to the fact that each  
163 clique corresponds to a full simplex so that a triangle is filled in. The set of  $k$ -holes defining a space is  
164 described by the  $k$ -th homology group  $H_k$ . Each  $k$ -hole  $i$  is in turn represented by its generator  $g_i^k \in H_k$ .  
165 Informally, generators are formed of elements of  $H_k$  that identify and can be used to construct the hole.

166

167 *Key concepts:* A clique complex is constructed from a network by identifying  $k$  cliques to  $k - 1$   
168 dimensional simplices. A clique complex can be described by its holes. A cycle is a hole of dimension 1  
169 (Fig. 1).

## 170 2.2.2 Homology

171 One of the most studied problems in mathematics is that of defining a notion of similarity between  
172 spaces. Intuitively, two spaces can be thought to be similar if we can transform one into the other via a  
173 well-behaved transformation. In particular, if there exists a continuous bijective map, a homeomorphism,  
174 that transforms one space into the other, then the two spaces are said to be homeomorphic. Such spaces are,  
175 informally, topologically the same, and any of their properties that are conserved by homeomorphism are  
176 are thus called *topological invariants*.

177

178 The homology group, or simply *homology*, is a property of a space which is based on the counting of  
179 holes and their associated dimensions. As an analogy to homology, the reader can think of *The Hound of*  
180 *the Baskervilles* by Sir Arthur Conan Doyle [17], where the non-manifestation of the hound one night was  
181 as informative to Sherlock Holmes as its presence. Homology is a topological invariant which, as explained  
182 above, means that it is a property of a space that is preserved by homeomorphisms and keeps the same  
183 value whatever the representation of the system (i.e. the bijective map used to look at it). Thus, if two  
184 spaces have the same homology, then they are topologically equivalent.

185

## 186 2.2.3 Persistent homology

187 The process of adding simplices to form a simplicial complex is called a filtration, and the filtration  
 188 we use in this paper is the *weight clique rank filtration* [32]. It has been specifically designed to extract  
 189 homological features from fully connected, weighted and signed networks. The filtration starts with a set  
 190 of disconnected nodes. Then all the edges from the original network are sorted in descending order of  
 191 magnitude and added one by one as 1-simplices to the complex. After each addition, the clique complex is  
 192 constructed and its persistent homology computed. When a new cycle appears, it is tagged with a "birth  
 193 time",  $\beta_i$  and when it disappears, it is tagged with a "death time",  $\delta_i$ . The difference between the two time  
 194 points defines its persistence  $\pi_i$ . It is important to note that when the starting network is fully connected, all  
 195 the cycles eventually die along the filtration. While it is true that the order in which edges are introduced  
 196 can depend on very small differences in the weights, the same small differences would alter the persistence  
 197 or appearance of generators by a similarly small value hence ultimately producing small variations in the  
 198 scaffold. This is a consequence of the robustness theorems for persistent homology, where one substitutes  
 199 the usual metric with an extended semi-metric[3, 9, 10].  
 200

201 *Key concept:* The persistence of each cycle is measured using weight rank filtration.

## 202 2.2.4 Homological scaffolds

203 The homological scaffolds are secondary networks and were introduced in [31] as a mean to summarise  
 204 part of the persistent homology of cycles information for the edges. As they localise the cycles on specific  
 205 edges of the network, they can naturally be seen as edge centrality measures that characterise the importance  
 206 of links in the original network through the filtration process, where the weights on the edges represent  
 207 their centrality.  
 208

209 Two scaffolds are introduced to highlight different aspects of the importance of an edge in the network:  
 210 the number of cycles an edge belongs to and the total persistence of the cycles it belongs to. The weights of  
 211 the edges are defined as:

$$\omega_e^f = \sum_{g_j} \mathbf{1}_{e \in g_j} \quad (1)$$

212 for the frequency scaffold  $H_G^f$ , and

$$\omega_e^p = \sum_{g_j | e \in g_j} \pi_{g_j}, \quad (2)$$

213 for the persistence scaffold  $H_G^p$ .  
 214

215 The information given by the scaffolds has to be interpreted with care, see section 2.2.6 below  
 216 for a full description of the limitations. The python library we developed for persistent homology  
 217 analysis, that includes the weight rank clique filtration and the scaffolds generation is available at:  
 218 <https://github.com/lordgrilo/Holes>.  
 219

220 *Key concept:* The homological scaffold measures the importance of edges relative to the number of cycles  
221 they belong to and the persistence of these cycles. The present study focuses exclusively on the *persistence*  
222 *scaffold*.

### 223 2.2.5 Example

224 Persistent homology and the computation of the scaffolds can be illustrated by a simple toy example,  
225 which is described in the following lines and shown graphically in Fig. 3. For simplicity, some of the  
226 edges have a weight of zero and are thus not represented. The first step is the filtration: edges are added  
227 in decreasing order of magnitude. In the example, edges have five different weights. Accordingly, five  
228 filtration steps are needed, and five associated clique complexes are formed. There are two cycles: one born  
229 at step 2) and one born at step 3). By contrast, the edge added at step 4) does not define a new cycle. The  
230 aforementioned cycles are both killed by the addition of the two edges at step 5). Their persistences are  
231 summarized in the barcode below the filtration. The resulting scaffolds are on the right of the barcode: the  
232 persistence scaffold (green) and frequency scaffold (blue). Inspecting the weights of both scaffolds, we  
233 conclude that edge  $\langle fc \rangle$  is the most important to support the homological structure of the network.

### 234 2.2.6 On the effect of the cycle representative

235 As illustrated by the present paper and [31], homological scaffolds can be quite informative, however  
236 there is a caveat one has to be aware of when interpreting the results: the choice of a cycle's representative.  
237 Persistent homology probes a dataset for its homological features that are persistent – more specifically  
238 in the case treated in this paper, cycles. Cycles are topological objects and thus their "sizes" are not  
239 uniquely defined, because the homology generators are defined as an equivalence class. Indeed, each cycle  
240 corresponding to a certain homology generator can be stretched and deformed, while still remaining a valid  
241 representative cycle. In practice, however, to identify homological properties of a topological space, one  
242 has to recourse to a representation of the components of the simplices that bound it. In this setting, a hole  
243 will be uniquely identified by the edges (or higher-dimensional simplices) forming its smallest boundary  
244 at the time of its birth. During the filtration process, a cycle will potentially shrink due to the addition of  
245 an edge. Although the shrinking has no topological meaning for the hole itself as it remains the same, its  
246 representation changes, i.e. the specific edges forming its boundary change. The question "what is the best  
247 representative of a cycle" is an open problem and the definition of *best* strongly depends on the problem at  
248 hand.

249

250 In practice, however, this will have an impact. We used the software package javaplex [39] in our pipeline  
251 for the implementation of persistent homology. It chooses a representative for a cycle and identifies it with  
252 the entire lifetime of the cycle. This means that a unique set of edges will represent a cycle, regardless of  
253 its possible contraction. This has a direct implication on the scaffolds, and means they are not well-defined.  
254 This does not mean they are not informative, but rather that care has to be taken when interpreting the  
255 meaning of the particular edges weight forming the scaffolds. The evolution of any cycle representative is a  
256 combination of two possible situations:

- 257 1. A cycle shrinks by triadic closure,
- 258 2. a cycle is split into 2 smaller cycles.

259 These two possibilities are illustrated in Fig. 4, case i) on the top and case ii) on the bottom. Therefore,  
260 one can monitor the original cycles' subgraphs evolutions as edges are added during the filtration to verify  
261 how the cycles die and correctly interpret the homological scaffolds.

262 Practically, this means exploring the statistics of the holes and verify how they close. It is also important  
 263 to note that the aforementioned phenomena are more likely to occur in cycles that are long lived.

### 264 2.3 Graph Theoretical Analysis

265 By construction, the graphs that we have considered for the standard graph analysis are unweighted,  
 266 undirected, and do not contain self-loops. Their adjacency matrix  $A$  is therefore symmetric, and its elements  
 267 are equal to 1 if nodes  $i$  and  $j$  are connected and zero otherwise.

#### 268 2.3.1 Standard Graph Metrics in Binarized Graphs

269 We now briefly introduce the standard local centrality measures that were applied to the networks: degree  
 270 centrality ( $DC$ ), betweenness-centrality ( $BC$ ), local efficiency ( $Eff$ ) and participation coefficient ( $PC$ ).  
 271 Standard graph measures were calculated using the *Brain Connectivity Toolbox* in Matlab [34]. These  
 272 metrics each capture different aspects of the contributions of a node to the network organization. To  
 273 facilitate the interpretation of standard graph metrics, functional connectivity matrices were binarized at  
 274 eleven statistical thresholds that give a network link density ( $D$ ) in the range  $[0.10, 0.60]$  in increments of  
 275 0.05, eliminating the weakest links in the network. This thresholding approach was performed using the  
 276 *threshold\_proportional* function of the *Brain Connectivity Toolbox*.

277

278 The degree centrality is a measure of the total number of connections that a node has. It therefore depends  
 279 on the direct neighborhood of the node. For a node  $j$  within a binarized network comprising  $N$  nodes,  
 280 degree centrality is defined as:

$$DC(j) = \sum_{i=1}^N A_{i,j} \quad (3)$$

281 The betweenness-centrality of a node measures how many of the shortest paths between all other node  
 282 pairs pass through it and is a measure of its importance when routing information in the network. By  
 283 contrast to the degree,  $BC$  is dependent of the overall topology of the rest of the network beyond the direct  
 284 neighborhood of a node. For a node  $k$  it is defined as:

$$BC(k) = \sum_{i \neq j \neq k, i, j=1}^N \frac{\hat{\sigma}_{i,j}(k)}{\hat{\sigma}_{i,j}} \quad (4)$$

285 where  $\hat{\sigma}_{i,j}(k)$  is the number of shortest paths going from node  $i$  to node  $j$  through node  $k$ , and  $\hat{\sigma}_{i,j}$  is the  
 286 total number of shortest paths going from node  $i$  to node  $j$ .

287 The local efficiency of a node  $k$  computes how well the neighbors of a node are connected together. That  
 288 is, the inverse of the average shortest path length connecting the neighbors of that vertex:

$$Eff(k) = \frac{2}{Nn(n-1)} \sum_{i \in G}^n \sum_{i < j \in G}^n \frac{1}{d_{i,j}} \quad (5)$$

289 where  $n$  is the number of neighbors of a node  $k$ .

290

291 In addition, a community detection algorithm based on modularity (*Louvain method with finetuning*[4])  
 292 was applied to the adjacency matrix with  $D = 0.40$ , and identified six communities for the partition

293 optimising the modularity function. The participation coefficient was then calculated for each node in  
 294 this network. The participation coefficient compares the degree of a given node to nodes in all other  
 295 communities with the number of links it has within its own cluster. Nodes with a high participation  
 296 coefficient are therefore expected to play an important role in binding different communities together and  
 297 hence contribute to global integration. This measure therefore provides additional information about a  
 298 node's role in the network topology which cannot be inferred from measures of topological centrality alone.  
 299 It is defined as:

$$PC_i = 1 - \sum_{c=1}^{N_C} \left( \frac{k_{C_i}}{k_i} \right)^2, \quad (6)$$

300 where  $k_i$  is the degree of node  $i$  and  $k_{C_i}$  its degree limited to cluster  $C$ .

### 301 2.3.2 Weighted Network Analysis

302 As a follow-up analysis, we explored the relationship between the *PSS* and the weighted counterparts  
 303 of the same three graph metrics employed in the original graph analysis described in section 2.3.1: the  
 304 nodal *strength* (weighted counterpart of degree), the weighted betweenness centrality (*wt - BC*) and  
 305 the weighted local efficiency (*wt - Eff*). By definition, the computation of these measures on a fully  
 306 connected weighted graph does not rely on the *ad hoc* thresholding of the FC matrix. The mathematical  
 307 formulation of the weighted version of the metrics are the same as in the unweighted case. For the nodal  
 308 strength, one sums up the weights of the links connected to a node:

$$SC(j) = \sum_{i=1}^N W_{i,j}. \quad (7)$$

309 For the weighted versions of betweenness centrality and efficiency, the difference resides in the definition  
 310 of the shortest path. In the BCT implementation, the shortest path is computed via a breadth-first search  
 311 algorithm that follows the links with the smallest weight [5].

### 312 2.3.3 Definition of PSS

313 Lastly, we define a new centrality measure for the homological scaffolds, the nodal *persistence scaffold*  
 314 *strength* (*PSS*). It is essentially the strength of a node, i.e. the sum of the weights of its links, in the  
 315 persistence scaffold  $H_G^p$ . We gave it a different name to clearly differentiate its meaning as a measure  
 316 obtained from the persistent homology procedure instead of pairwise interactions between edges and  
 317 vertices. It is defined as:

$$PSS(j) = \sum_{i=1}^N H_{G,i,j}^p \quad (8)$$

318 The *PSS* thus compresses into a scalar information about the persistence of cycles passing through a given  
 319 node. The *PSS* may thereby effectively capture the combination of a nodes central position in the network  
 320 and the relative lack of connectivity amongst its local neighbourhood. Moreover, as outlined above, the  
 321 *PSS* does not rely on *ad hoc* thresholding of the functional connectivity matrix and therefore includes  
 322 information from all the edges in the network. This is an important distinction between the *PSS* and the  
 323 topological centrality metrics traditionally measures applied to functional neuroimaging data.

#### 324 2.3.4 Definition of Functional Hubs

325 Node-level values were calculated for the *PSS* measure as well as standard graph centrality measures.  
326 As indicated above, the *PSS* does not require *a priori* thresholding of the functional connectivity matrix.  
327 However, for the computation of local graph measures (*DC*, *Eff* and *BC*), we calculated the node-level  
328 metric values at each of eleven different thresholds over the  $D = [0.10, 0.60]$  range. This curve was then  
329 integrated to yield a single nodal metric value that is independent of the threshold. The highest-ranking  
330 nodes (termed "hubs" for concision) were then identified for each of measure under study. They were  
331 defined as those nodes with a metric value larger than 1 standard deviation from the mean of their respective  
332 distribution.  
333

### 3 RESULTS

#### 334 3.1 Relationship between nodal *PSS* and standard graph metrics

##### 335 3.1.1 Topological centrality in binary networks

336 The main objective of this analysis was to examine the relationship between standard topological centrality  
337 measures described above; *DC*, *BC*, *Eff* and the nodal *PSS*. This was done by computing bivariate  
338 correlations between the standard graph metric values and nodal *PSS* across the threshold range applied to  
339 the functional connectivity matrix. The *R*-values and *p*-values for each analysis are listed in supplementary  
340 figures S1a and S1b. It is important to note that while different FC network thresholds were used for  
341 the standard graph analysis, the input FC matrix for the persistent homology analysis did not require *a*  
342 *priori* thresholding, which is a potential strength of this methodology. In order to verify that the reported  
343 associations between nodal *PSS* and standard metric values at a given threshold were not simply driven by  
344 the direct connectivity of network nodes, we also examined the correlations *DC* vs *BC*, *DC* vs *Eff* and  
345 *BC* vs *Eff* as control conditions (Fig. 5).

346 *PSS* vs *DC*: The positive correlation between *PSS* and *DC* was significant at all thresholds under  
347 study, although it was consistently weaker than the correlation of *PSS* vs *BC*.

348 *PSS* vs *BC*: The *PSS* showed strong and also statistically significant positive correlations with the *BC*  
349 metric at all thresholds under study. This indicates that *PSS* is associated with a node's tendency to be  
350 part of shortest paths between node pairs in the network.

351 *PSS* vs *Eff*: Conversely, a strong and significant *negative* correlation was observed between the *PSS*  
352 and *Eff* metrics at all but one threshold, showing that high *PSS* nodes generally avoid densely connected  
353 neighborhood clusters. These results are illustrated in the top panel of Figure 5.

354 *DC* vs *BC*: By contrast to *PSS* vs *BC*, the *DC* vs *BC* correlation failed to reach statistical significance  
355 at 5 of the 11 thresholds under study. When the relationship did reach statistical significance at some of the  
356 higher network densities, the *DC* vs *BC* correlations remained on average weaker than *PSS* vs *BC* over  
357 the same threshold range.

358 *DC* vs *Eff*: The *DC* vs *Eff* correlation also showed a threshold-dependent profile. Significant positive  
359 correlations were observed at some of the lower densities in the  $D = [0.1, 0.2]$  range which contrasted with  
360 the *negative* correlations between *PSS* vs *Eff* observed at these same thresholds. *DC* vs *Eff* did not  
361 reach statistical significance at any of the thresholds exceeding  $D > 0.35$ .

362 *BC vs Eff*: Finally, the negative correlation between the *BC* and *Eff* metrics was qualitatively similar  
363 to the *BC vs PSS* correlation over the threshold range. However, *BC vs Eff* did not reach statistical  
364 significance at the lowest network density of  $D = 0.1$  and the negative correlation strengths at higher  
365 densities were overall stronger (and less stable) for *BC vs Eff* than *PSS vs BC*. These results are  
366 graphically represented in the bottom panel of Figure 5.

### 367 3.1.2 Topological centrality in weighted networks

368 As a follow-up analysis, the relationships between the *PSS* and the weighted counterparts of the  
369 metrics used in the original analysis were also studied. These included the nodal *strength*, weighted  
370 betweenness-centrality (*wt - BC*) and weighted efficiency (*wt - Eff*).

371 *strength vs PSS*: There was a borderline significant positive correlation between the nodal strength in  
372 the weighted network and the *PSS*:  $R = 0.21$ ,  $n = 90$ ,  $p = 0.046$ .

373 *wt - BC vs PSS*: The positive correlation between *wt - BC vs PSS* was stronger than *strength vs*  
374 *PSS* and highly significant:  $R = 0.39$ ,  $n = 90$ ,  $p < 0.01$ ; consistent with the results of the binary graph  
375 analysis.

376 *wt - Eff vs PSS*: There was a significant *positive* correlation between *PSS vs wt - Eff*:  $R = 0.23$ ,  
377  $n = 90$ ,  $p = 0.03$ . This relationship was opposite to that observed in the binary network analysis where  
378 *PSS vs Eff* instead showed a strong *negative* association at all thresholds under study.

### 379 3.1.3 Participation Coefficient

380 For the network with an intermediate density of  $D = 0.40$ , a community detection algorithm was applied  
381 to the data and the participation coefficient (*PC*) was computed for each node in the network. A significant  
382 positive correlation was revealed between *PC* and *PSS*,  $R = 0.32$ ,  $n = 90$ ,  $p < 0.01$ . This indicated that  
383 the *PSS* measure also reflects the tendency of a node to act as a bridge across communities in distributed  
384 brain networks.

## 385 3.2 Identification of functional hubs using the *PSS* and standard graph measures

386 We now explain the results shown in Fig. 6 and Fig. 7. Functional hubs were identified on each of the  
387 *PSS*, *DC*, *Eff* and *BC* measures using the procedure outlined in section 2.3.4. Fourteen AAL regions  
388 (out of 90) were identified as hubs on the *PSS* measure. The most important overlap was observed between  
389 the *PSS*-hubs and the *DC*-hubs (5/14) and the second-most important overlap was between the *PSS*-hubs  
390 and *BC*-hubs (4/14). We note that this was the case despite the presence of a stronger positive correlation  
391 between *PSS vs BC* than *PSS vs DC* at all the thresholds under consideration. As expected, *Eff*-hubs  
392 showed the least amount of overlap with the *PSS*-hubs, consistent with the strong negative correlation  
393 between these two measures.

## 4 DISCUSSION

394 Persistent homology provides a window into the global organization of the edges' weights fabric of a  
395 graph. The present results indicate that persistence homological scaffolds may be useful objects to consider  
396 in functional neuroimaging research. The persistence scaffold notably circumvents the need for *ad hoc*  
397 thresholding of the functional connectivity matrix and is constructed using the data of all the edges present  
398 in the original network. Moreover, the concept of *simplicial complexes* upon which the persistence scaffold  
399 is built allows one to describe relations between distributed sub-populations of network elements consistent

400 with the brain's encoding of information in distributed networks, and is not restricted to dyadic associations  
401 between region pairs.

402

403 In order to study the relationship between standard network metrics and on the persistence homological  
404 scaffold, we calculated the strength of each node in the persistence scaffold and termed this novel measure  
405 the persistence scaffold strength (*PSS*). The *PSS* measure hence differs in important ways from the  
406 standard graph metrics used in neuroimaging studies as it includes information from seemingly unimportant  
407 edges with weak weights in the network, and considers the contributions of mesoscopic structures ("cycles")  
408 to the network organization, rather than edge-vertex interactions. We then examined how *PSS* relates to  
409 some of the local binarized and weighted graph theoretical metrics typically employed in neuroimaging  
410 studies.

411

412 Of the binary graph metrics under study, *PSS* showed the strongest positive correlation with the  
413 betweenness-centrality metric (*BC*) across the entire threshold range. Even when controlling for the node  
414 degree by means of a partial correlation analysis, the positive association between *PSS* and *BC* remained  
415 highly significant. This suggested that high *PSS* nodes are likely to contribute to the binding of information  
416 across different sources in the brain by creating shortest paths between node pairs. Conversely, a strong  
417 negative correlation was observed between *PSS* and local efficiency (*Eff*), and indicates that nodes  
418 with a high *PSS* are unlikely to participate in strongly integrated local networks. To further explore the  
419 association between the *PSS* measure and functional integration, we conducted a modularity analysis and  
420 computed the participation coefficient (*PC*) of network nodes. A strong positive correlation between *PC*  
421 and *PSS* was found in the network under study. Nodes with a high participation coefficient preferentially  
422 make connections to network communities other than their own, consistent with network roles in global  
423 integration.

424 Taken together, these observations lead to an understanding of the meaning of this new centrality measure  
425 and on the interpretation of persistent homological scaffold. The tendency of high *PSS* nodes to bind  
426 topologically remote modules in the brain whilst simultaneously avoiding clustered neighbourhood reflects  
427 the significance of persistent homology in resting-state fMRI data. *PSS* therefore captures different aspects  
428 of global network organisation in a natural index that does not rely on any weighted average of classic  
429 graph metrics, and that extracts this information directly from the data. We also note that although for  
430 interpretational purposes we limited ourselves to the study of the first homology group, the *persistence*  
431 *scaffold strength* can easily be generalised to higher dimensions, where it would capture aspects of the  
432 network organisation that are not reflected at all by traditional network metrics.

433 When bypassing the thresholding step and instead comparing the *PSS* to the *weighted* counterparts  
434 of the standard graph measures computed on the fully connected network, the results for *strength* and  
435 *wt - BC* were broadly consistent with those of the binarized networks. As in the binary network analysis,  
436 the *strength vs PSS* correlation was positive and significant, but weaker than the *wt - BC vs PSS*  
437 correlation. However a significant *positive* correlation was observed for the *PSS vs wt - Eff* correlation  
438 in the weighted network, which was inconsistent with the results of the thresholded network analysis where  
439 the binarized version of the two metrics were actually *negatively* correlated at every threshold under study.  
440 This exemplifies that the generalisation of a binary graph metric to a fully connected weighted network  
441 does not imply its specialization.

442 Finally, we note that the nodal *PSS* does not merely recapitulate the betweenness-centrality metric.  
443 Although the correlation between *PSS* and *BC* measures was significant at all thresholds under study in  
444 the binary networks analyses, only 4 of the 14 highest ranking *PSS* nodes overlap with the hubs identified  
445 on the *BC* metric (Fig. 6). This may be explained by the fact that some nodes ranking highly on the  
446 betweenness-centrality metric concurrently participate in strongly connected neighborhood clusters; their  
447 respective edges would thus form clique complexes at an early stage in the filtration, leading to low *PSS*  
448 value. Moreover, the value of the correlation between *PSS* and *BC* was around  $R = 0.4$  in both the  
449 binarized and weighted network analyses, which further suggests that the *PSS* and *BC* do not reflect  
450 identical network attributes.

451 The highest-ranking regions on the *PSS* measure (Figs 6-7) were distributed across the brain, consistent  
452 with potential roles in the global integration of local networks. There was nevertheless a tendency for the  
453 *PSS* hubs to belong to frontal cortical areas (middle & superior frontal gyri, precentral gyrus, rolandic  
454 operculum, cingulate), and subcortical structures (amygdala, globus pallidum, caudate nucleus). In the  
455 posterior brain, *PSS*-hubs within the parietal lobe included the inferior and superior divisions of the  
456 parietal gyrus but did not include midline parietal structures. In the occipital lobe, a visual association area  
457 located in the superior occipital cortex ranked highly as a *PSS* hub, as did the calcarine fissure which  
458 includes part of the primary visual cortex (V1). We note that V1, which also ranked highly on the *DC*  
459 metric in this study, has previously been shown to engage in distributed networks thought to support mental  
460 imagery during the resting-state [43]. Interestingly, no subdivision of the temporal cortices were included  
461 amongst *PSS*-hubs, despite several of these regions ranking highly on the *DC* measure.

462

463 We also paid attention to the special case of high-ranking *PSS* nodes which did **not** qualify as "hubs"  
464 on any of the three standard topological centrality measures (*DC*, *Eff*, *BC*). This subset of nodes was  
465 anatomically restricted to the lateral frontal and parietal cortices. They included the middle and superior  
466 frontal gyri, as well as inferior and superior sections of parietal gyri. These findings would suggest that,  
467 relative to standard topological centrality metrics, the *PSS* may be particularly sensitive to the network  
468 activity of frontal and parietal association areas located on the lateral surface of the brain. This would be  
469 consistent with the established role of these regions towards supporting high-level cognitive and behavioral  
470 functions requiring the large-scale coordination of network elements. The relative importance of *PSS*-hubs  
471 towards the information processing capacities of the brain should notably be assessed in future studies by  
472 means of virtual lesions in whole-brain computational models [13, 14, 42].

473

474 It has now become well recognized that the brain performs local computations in segregated modules  
475 that become seamlessly integrated over space and time to support high-level functions necessary for  
476 survival. Some brain regions are likely to play a more critical role than others towards enabling the global  
477 integration of information. The exact identities of these regions and the optimal experimental approaches  
478 for identifying them remain unclear. However recent evidence would suggest that integrative nodes, such  
479 as those potentially identified via the persistence homological scaffold, require metastability for maximal  
480 exploration of the full dynamic repertoire of the brain [22]. Previous research has employed diffusion tensor  
481 imaging (DTI) and graph theoretical analysis to identify a subset of hubs which forms a central core or  
482 "rich-club" that has been suggested to be important for global brain integration by linking together spatially  
483 remote network communities [41]. Yet, the mapping of a structural network architecture that can plausibly  
484 support segregation and integration does not describe the causal mechanisms and/or activity dynamics that  
485 actually underlie functional segregation and integration of information [14]. The identification of integrator

486 hubs directly from *functional* neuroimaging data using the homological scaffold may be particularly  
487 valuable in this regard.

488

489 The application of computational topology analysis to functional neuroimaging data is a novel avenue of  
490 research, and the physiological significance of homological scaffolds and related measures remains unclear.  
491 Given that high *PSS* nodes participate in a large proportion of cycles along the filtration, such nodes  
492 may be well positioned to contribute to a specific type of integration where, for example, a given neural  
493 pathway diverges than re-converges. Examples of such pathways include the dorsal/ventral visual streams  
494 and the well-defined cortico-basal loops between the basal ganglia and motor cortex. Further studies will  
495 be needed to test these hypotheses with specificity, but we nevertheless point out that the identification of  
496 both visual areas as well as basal ganglia and cortical motor areas amongst the *PSS*-hubs in the present  
497 analysis supports this idea.

498

499 Whilst the present results suggest that high-ranking *PSS* nodes could be well positioned to support the  
500 integration of information across segregated brain modules, further studies will be needed to confirm this  
501 observation. One potential approach would be to apply recently developed measures of perturbational  
502 integration and segregation in a whole-brain computational model. Previous work has shown that, by  
503 perturbing *in silico* neural dynamics by a random set of Gaussian inputs, one can estimate and the amount  
504 of integration in the system calculated after each perturbation. In this context, perturbational integration  
505 is defined by considering the length of the largest connected component of the functional network as an  
506 estimate of the amount of integration in the system after each perturbation, as described in detail in [14].  
507 One would therefore expect virtual lesions to high-*PSS* nodes to have a particularly profound impact on the  
508 system's integration capabilities, relative to randomly selected network nodes. Another possibility would  
509 be to investigate changes in *PSS* hubs assignment and distributions in clinical syndromes characterized by  
510 disordered functional integration at the whole-brain scale, such as schizophrenia[25, 1]. Both approaches  
511 could help determine to what extent *PSS*-hubs support the integration of network elements, and potentially  
512 provide useful insights into the neurobiological attributes of topologically central brain regions in the  
513 homological scaffold.

514

515 Another limitation of this study, as mentioned in section 2.2.6, is the choice of the representative cycles  
516 for homology classes, which could result in selecting edges that do not belong to the shortest cycle around  
517 a certain hole. A possible way around this limitation would be to perform an *a posteriori* analysis of  
518 the cycles, in which one controls for the evolution of the subgraph's transitivity (as done in [31]). One  
519 could also consider employing computationally cumbersome techniques to track the shortest path across  
520 the filtration and then update the scaffold accordingly [16, 15]. Further work is needed to establish which  
521 protocol would be most suited to the specific case of fMRI networks. Our results on network communities  
522 nevertheless suggest that the cycle choice issues might not be so critical in our study and potentially lead to  
523 a stronger *PSS* interpretation. Indeed network communities, being densely connected internally and strong  
524 information integrators, likely constitute the network regions where connected triangle components reside  
525 and thus the regions where different representative cycle choices are possible. Moreover, scaffold hubs  
526 already tend to have large participation coefficients suggesting that they behave as information brokers  
527 between these communities and are therefore, although imperfectly, capturing the large-scale homological  
528 structure.

529 In summary, the present study has explored the relationship between standard network metrics in  
530 functional brain network and the persistence homological scaffold derived from the same fMRI dataset.  
531 The computation of a local graph measure on the persistence homological scaffolds (*PSS*) differs from  
532 standard applications of graph theory to functional neuroimaging data as the scaffolds are not derived  
533 from typical dyadic interactions between network elements, and consider information from all edges in  
534 the network. The results suggest that topologically central nodes in the persistence scaffold may play  
535 important roles towards supporting the functional integration of information across brain modules. Future  
536 work should investigate the sensitivity of the homological scaffolds and derived measures to disease-related  
537 changes in brain function as well as the specific type of integration performed by the strongest edges and  
538 nodes in the scaffolds.

## DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

539 The authors declare that the research was conducted in the absence of any commercial or financial  
540 relationships that could be construed as a potential conflict of interest.

## AUTHOR CONTRIBUTIONS

541 L-D.L., P.E., M.L.K., F.E.T. designed the study. T.V.H., H.M.F., M.L.K. collected and processed the  
542 fMRI data. P.E., G.P., F.V. developed and implemented the persistence homological scaffolds methodology  
543 essential to this study. L-D.L., H.M.F. performed the graph theoretical analysis of the data. P.E., L-D.L.,  
544 T.V.H. made the figures. P.E., G.P., F.V. and L-D.L. wrote the methods section. L-D.L. wrote the results  
545 section. L-D.L. and P.E. wrote the introduction and discussion sections, with editorial guidance from  
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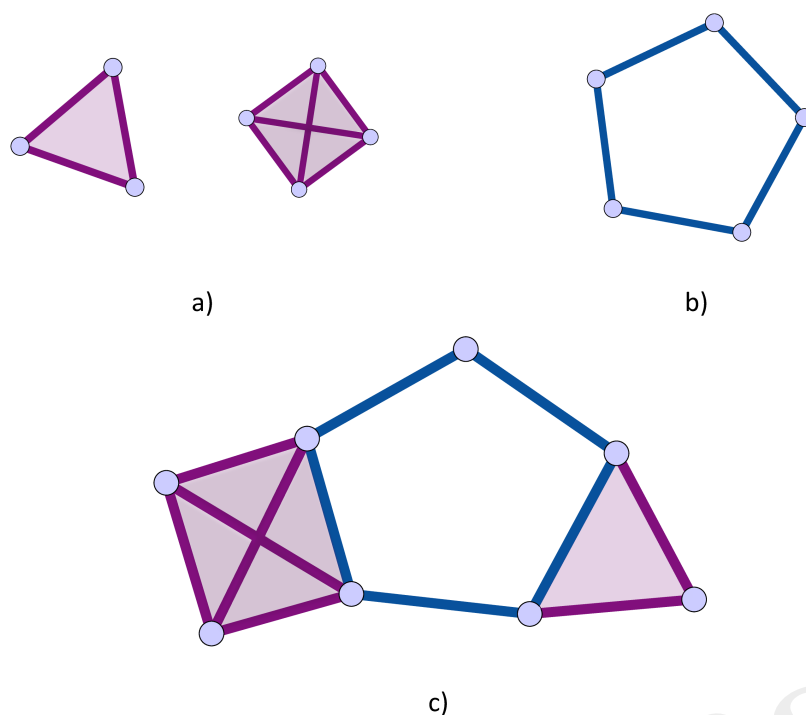
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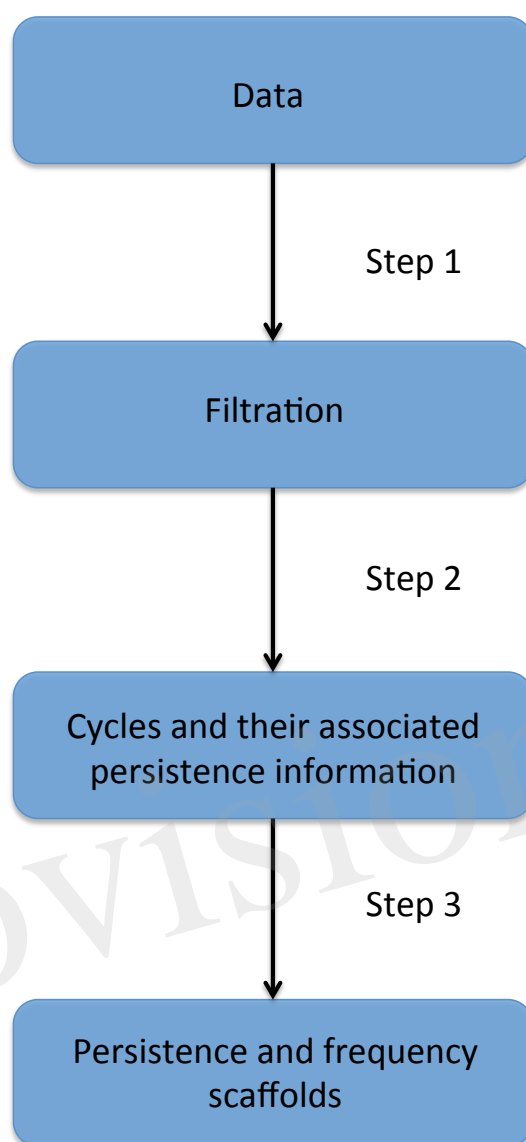
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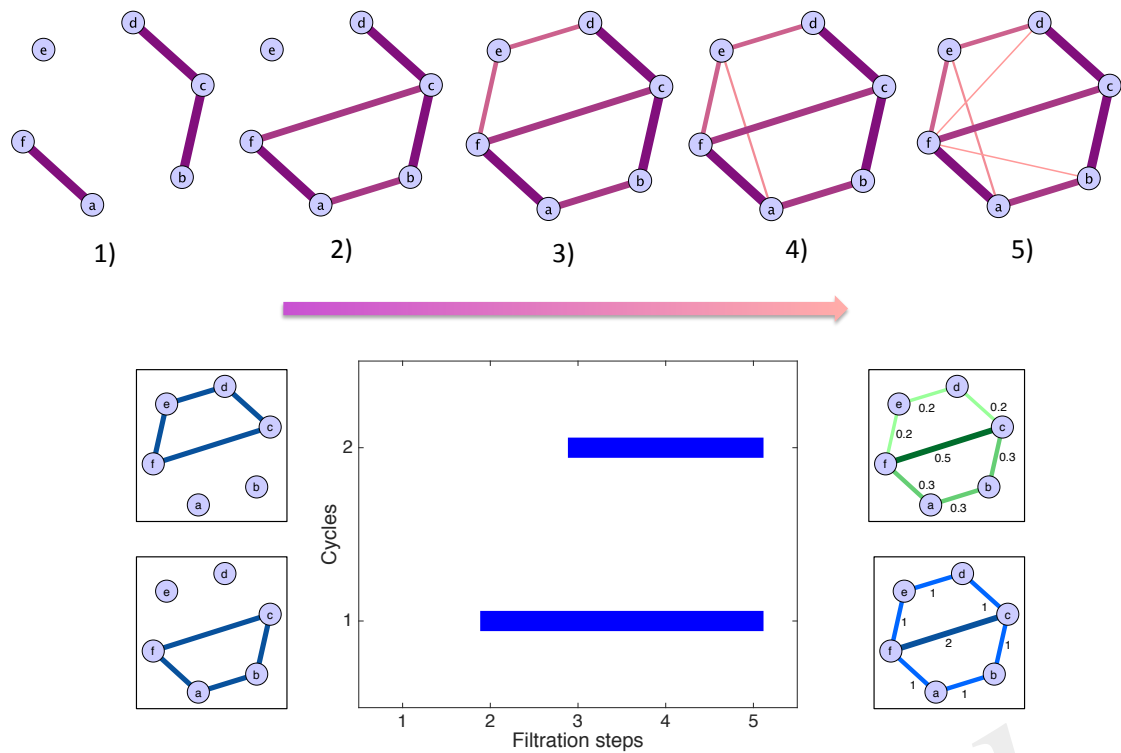
## FIGURES



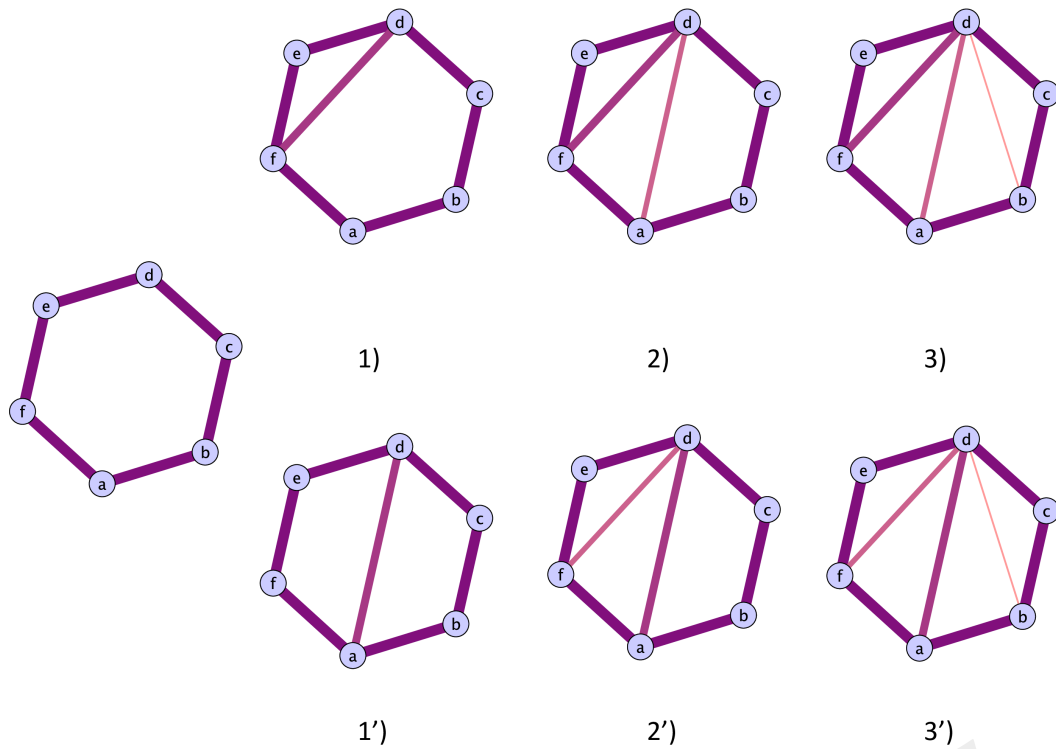
**Figure 1.** Illustrations of cliques, simplices, holes and clique complex. The simplices are shaded for identification. **a)** 3 and 4-cliques, which are associated to 2 and 3-dimensional simplices. **b)** a 1-dimensional hole, or cycle, is a closed path of edges of length greater than 3. **c)** Combining the elements of a) and b) following the rules in 2.2.1, one can produce a clique complex with one 1-dimensional hole. All simplices in this figure are shaded as is customary.



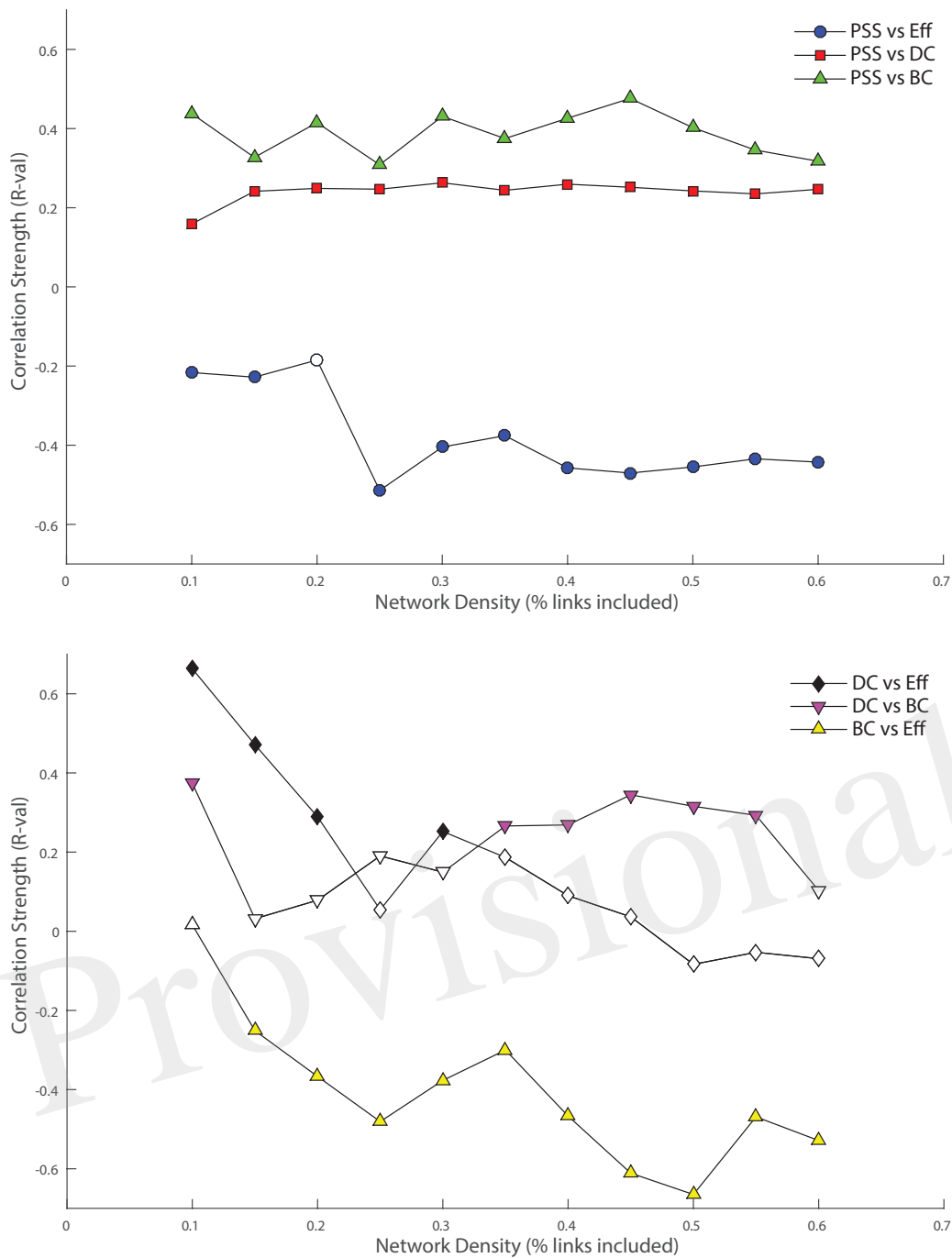
**Figure 2.** Description of the four stages of the persistent homology and homological scaffolds analysis workflow. **The data** consist of a fully connected weighted network. **The filtration** is produced using the weight clique rank filtration. **The persistent homology** of the filtration is computed, and each cycle (or 'hole') is endowed with a birth and death time. **The homological scaffolds** are generated using the information from persistent homology



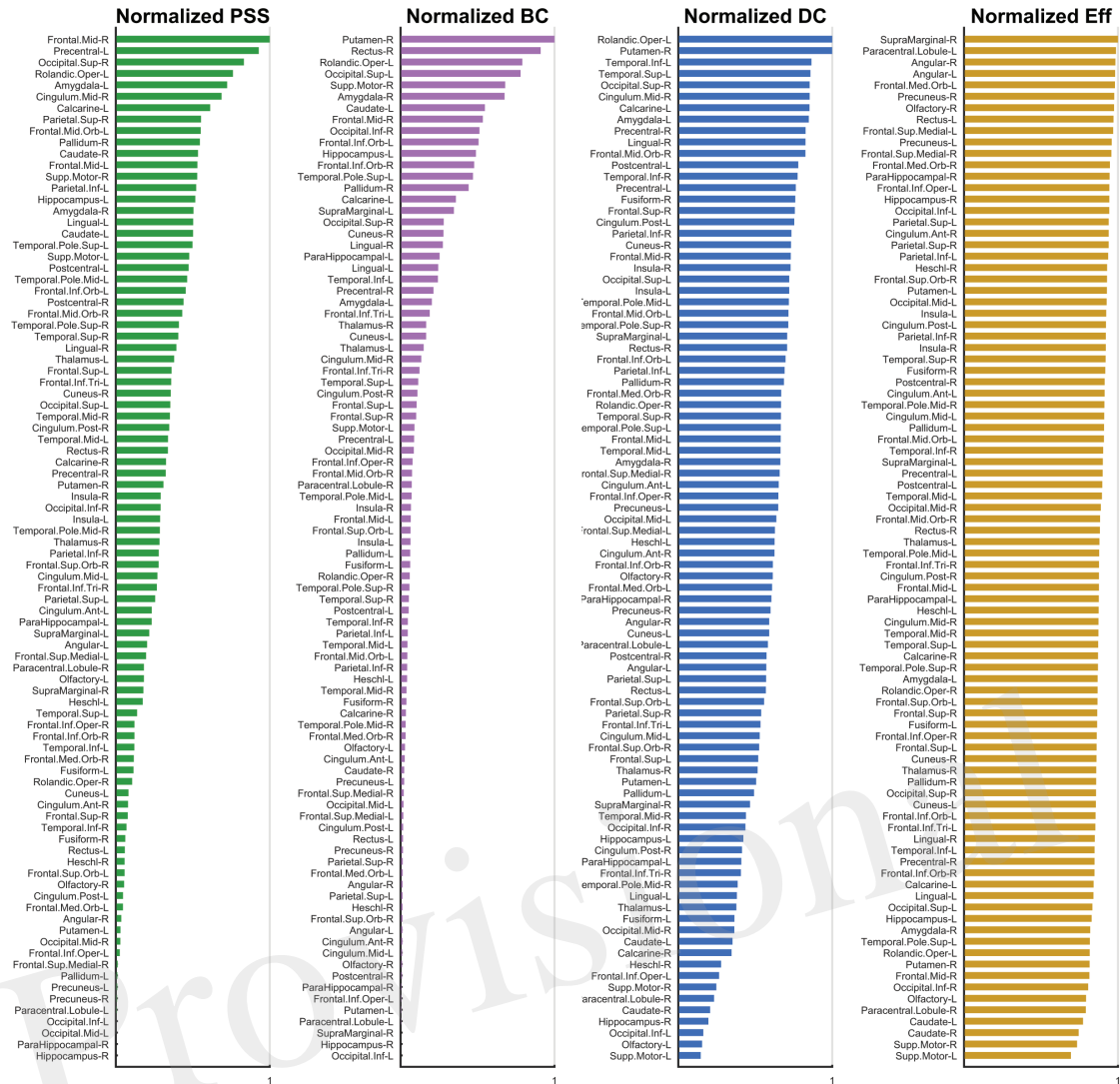
**Figure 3.** Toy example illustrating the generation of the homological scaffolds. **On top** The filtration: edges are added in decreasing order of weight (thickness and colour represent the weights) to arrive at the original network at step 5). **Bottom middle** The barcode encoding the persistence of the two cycles  $\langle abc f \rangle$  and  $\langle cde f \rangle$ . **Bottom right** The persistence (green) and frequency (blue) scaffolds, summarising the role of the edges in the cycles present during the filtration.



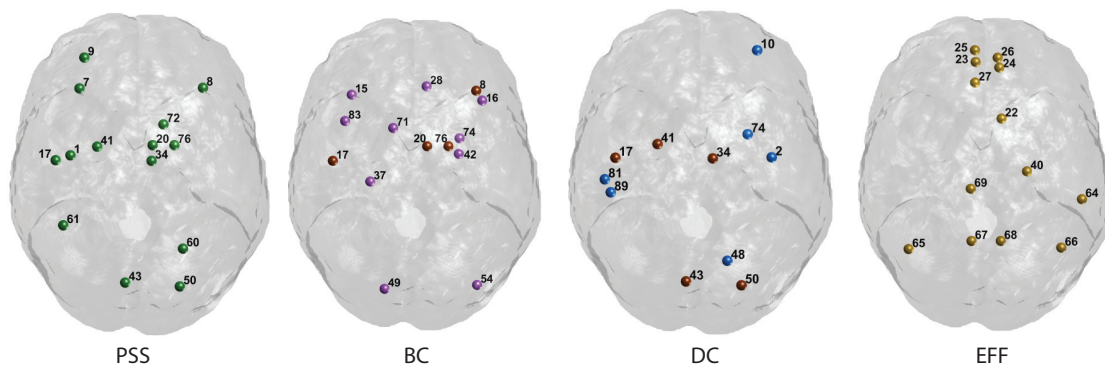
**Figure 4.** Illustration of the two possible routes a cycles can close. **Top route:** The cycles closes with the addition of triangles. The cycles representative will be the original cycles  $\langle abcdef \rangle$ , irrespectively of the life time of the sub cycles that are partially closed. **Bottom route:** The original cycle is split into smaller cycles that are eventually closed by the mechanism illustrated in the top route. The two cycles that will be represented in the original cycle  $\langle abcdef \rangle$  and the subcycle  $\langle abcd \rangle$ , as the cycle  $\langle adef \rangle$  can be obtained as a linear combination of the first two



**Figure 5. Top:** Relationship between nodal persistence scaffold strength (*PSS*) and standard topological centrality measures. At each threshold under study, the value of the bivariate correlation coefficient (*R*) between *PSS* and each of: degree-centrality (*DC*), betweenness-centrality (*BC*) and local efficiency (*Eff*) is plotted. **Bottom.** Relationship between standard topological measures. The same procedure as above is repeated for correlations between: *DC* vs *BC*, *DC* vs *Eff*, and *BC* vs *Eff* as control conditions. **Filled shapes** indicate the presence of a **statistically significant** correlation between the two variables ( $p < 0.05$ ).



**Figure 6.** Normalized Metric Values. The normalized nodal values are displayed for each graph measure under study. The values for *PSS*, *BC*, *DC* and *Eff* are respectively depicted from left to right. While computation of the *PSS* does not require *ad hoc* thresholding, the *BC*, *DC* and *Eff* metrics are threshold-dependent and nodal metric values have thus been integrated over the threshold range under study to generate a single value for each node. The analysis used is described in detail section 3.2



**Figure 7.** Graphical Display of the Highest-Ranking Nodes. Functional hubs identified on the *PSS* measure and three standard topological centrality metrics (*BC*, *DC*, *Eff*). Hubs on each measure are defined as having a value  $>1$  S.D. of the mean of their respective distribution. Nodes overlapping with the *PSS* hubs are shown in brown. The corresponding AAL labels for each numerical index are included in supplementary figure S2.

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