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

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2 ABSTRACT

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

23 persistence homological scaffold by computing the strength of each node in the scaffold and

comparing it to local graph metrics traditionally employed in neuroimaging studies. We conclude that the persistence scaffold enables the identification of network elements that may support the

that the persistence scaffold enables the identification of network elements that m
 functional integration of information across distributed brain networks.

27

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

1 INTRODUCTION

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

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

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

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

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

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

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

2 MATERIAL & METHODS

97 2.1 Data

98 2.1.1 Study Participants

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

in accordance with the Declaration of Helsinki ethical principles for medical research and ethics approval
was granted by the Research Ethics Committee of the Central Denmark Region (De Videnskabsetiske
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 mm³; reconstructed matrix size 256x256; 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°, reconstructed matrix size = 111 96x96, voxel size 2x2 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 performed using the FSL toolbox (www.fmrib.ox.ac.uk/fsl, FMRIB, Oxford) [37]. The EPI image was 117 118 co-registered to the T1-weighted structural image, and the T1-weighted image was coregistered to the T1 template of ICBM152 in MNI space. The resulting transformations were concatenated and inversed and 119 further applied to warp the AAL template from MNI space to the EPI native space, where interpolation 120 using nearest-neighbor method ensured that the discrete labelling values were preserved. Initial fMRI data 121 preprocessing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL and 122 consisted of: motion correction using MCFLIRT; non-brain tissue removal using BET; spatial smoothing 123 124 using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line 125 fitting, with sigma = 50.0s). 126

127 2.1.4 Functional Connectivity Analysis

We used FSL to extract and average the time courses from all voxels within each AAL cluster. We then used Matlab (The MathWorks Inc.) to compute the pairwise Pearson correlation between all 90 regions. *R*-values were transformed to *z*-values via Fisher transformation, and the resulting *z*-values composed the final 90x90 functional connectivity (FC) matrix. We averaged the FC matrices for all 16 participants to obtain a group-averaged 90x90 FC matrix.

133 2.2 Persistent homology and scaffolds

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

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

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

There are many types of simplicial complexes. In this study, we focus on *clique complexes*, which can 154 155 be constructed from any network. In graph theory, a *clique* is a subset of vertices of a graph in which every pair of vertices is adjacent. Thus a k-clique is a completely connected subgraph $K_k \subset G$, composed 156 157 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 simplices in a clique complex, structures called *holes* can remain, and these are the structures of interest 159 160 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 complex, a cycle is a minimal closed path of length greater than 3 (Fig. 1). This is due to the fact that each 162 163 clique corresponds to a full simplex so that a triangle is filled in. The set of k-holes defining a space is described by the k-th homology group H_k . Each k-hole i is in turn represented by its generator $g_i^k \in H_k$. 164 Informally, generators are formed of elements of H_k that identify and can be used to construct the hole. 165 166

167 *Key concepts*: A clique complex is constructed from a network by identifying k cliques to k - 1168 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

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

177

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

185

186 2.2.3 Persistent homology

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

200

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

202 2.2.4 Homological scaffolds

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

208

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

$$\omega_e^f = \sum_{g_j} \mathbf{1}_{e \in g_j} \tag{1}$$

212 for the frequency scaffold H_G^f , and

$$\omega_e^p = \sum_{g_j \mid e \in g_j} \pi_{g_j},\tag{2}$$

213 for the persistence scaffold H_G^p .

214

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

219

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

223 2.2.5 Example

224 Persistent homology and the computation of the scaffolds can be illustrated by a simple toy example, which is described in the following lines and shown graphically in Fig. 3. For simplicity, some of the 225 226 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 filtration steps are needed, and five associated clique complexes are formed. There are two cycles: one born 228 229 at step 2) and one born at step 3). By contrast, the edge added at step 4) does not define a new cycle. The aforementioned cycles are both killed by the addition of the two edges at step 5). Their persistences are 230 summarized in the barcode below the filtration. The resulting scaffolds are on the right of the barcode: the 231 persistence scaffold (green) and frequency scaffold (blue). Inspecting the weights of both scaffolds, we 232 233 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 there is a caveat one has to be aware of when interpreting the results: the choice of a cycle's representative. 236 237 Persistent homology probes a dataset for its homological features that are persistent – more specifically in the case treated in this paper, cycles. Cycles are topological objects and thus their "sizes" are not 238 uniquely defined, because the homology generators are defined as an equivalence class. Indeed, each cycle 239 corresponding to a certain homology generator can be stretched and deformed, while still remaining a valid 240 representative cycle. In practice, however, to identify homological properties of a topological space, one 241 has to recourse to a representation of the components of the simplices that bound it. In this setting, a hole 242 will be uniquely identified by the edges (or higher-dimensional simplices) forming its smallest boundary 243 at the time of its birth. During the filtration process, a cycle will potentially shrink due to the addition of 244 245 an edge. Although the shrinking has no topological meaning for the hole itself as it remains the same, its representation changes, i.e. the specific edges forming its boundary change. The question "what is the best 246 representative of a cycle" is an open problem and the definition of best strongly depends on the problem at 247 hand. 248

249

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

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

These two possibilities are illustrated in Fig. 4, case i) on the top and case ii) on the bottom. Therefore, one can monitor the original cycles' subgraphs evolutions as edges are added during the filtration to verify how the cycles die and correctly interpret the homological scaffolds. Practically, this means exploring the statistics of the holes and verify how they close. It is also important to note that the aforementioned phenomena are more likely to occur in cycles that are long lived.

264 2.3 Graph Theoretical Analysis

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

268 2.3.1 Standard Graph Metrics in Binarized Graphs

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

277

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

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

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

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

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 total number of shortest paths going from node *i* to node *j*.

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

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

289 where n is the number of neighbors of a node k. 290

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

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

$$PC_{i} = 1 - \sum_{c=1}^{N_{C}} \left(\frac{k_{C_{i}}}{k_{i}}\right)^{2},$$
(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

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

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

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

312 2.3.3 Definition of PSS

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

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

The PSS thus compresses into a scalar information about the persistence of cycles passing through a given node. The PSS may thereby effectively capture the combination of a nodes central position in the network and the relative lack of connectivity amongst its local neighbourhood. Moreover, as outlined above, the PSS does not rely on *ad hoc* thresholding of the functional connectivity matrix and therefore includes information from all the edges in the network. This is an important distinction between the PSS and the 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. As indicated above, the *PSS* does not require *a priori* thresholding of the functional connectivity matrix. 326 However, for the computation of local graph measures (DC, Eff and BC), we calculated the node-level 327 metric values at each of eleven different thresholds over the D = [0.10, 0.60] range. This curve was then 328 integrated to yield a single nodal metric value that is independent of the threshold. The highest-ranking 329 330 nodes (termed "hubs" for concision) were then identified for each of measure under study. They were defined as those nodes with a metric value larger than 1 standard deviation from the mean of their respective 331 distribution. 332

333

3 RESULTS

334 3.1 Relationship between nodal PSS and standard graph metrics

335 3.1.1 Topological centrality in binary networks

The main objective of this analysis was to examine the relationship between standard topological centrality 336 measures described above; DC, BC, Eff and the nodal PSS. This was done by computing bivariate 337 correlations between the standard graph metric values and nodal PSS across the threshold range applied to 338 the functional connectivity matrix. The *R*-values and *p*-values for each analysis are listed in supplementary 339 figures S1a and S1b. It is important to note that while different FC network thresholds were used for 340 the standard graph analysis, the input FC matrix for the persistent homology analysis did not require a 341 priori thresholding, which is a potential strength of this methodology. In order to verify that the reported 342 associations between nodal PSS and standard metric values at a given threshold were not simply driven by 343 the direct connectivity of network nodes, we also examined the correlations DC vs BC, DC vs Eff and 344 345 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 BC349 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.

PSS vs Eff: Conversely, a strong and significant *negative* correlation was observed between the PSSand Eff metrics at all but one threshold, showing that high PSS nodes generally avoid densely connected 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

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

strength vs PSS: There was a borderline significant positive correlation between the nodal strength in 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

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

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

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

4 DISCUSSION

Persistent homology provides a window into the global organization of the edges' weights fabric of a graph. The present results indicate that persistence homological scaffolds may be useful objects to consider in functional neuroimaging research. The persistence scaffold notably circumvents the need for *ad hoc* thresholding of the functional connectivity matrix and is constructed using the data of all the edges present in the original network. Moreover, the concept of *simplicial complexes* upon which the persistence scaffold is built allows one to describe relations between distributed sub-populations of network elements consistent with the brain's encoding of information in distributed networks, and is not restricted to dyadic associationsbetween region pairs.

402

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

411

Of the binary graph metrics under study, PSS showed the strongest positive correlation with the 412 betweenness-centrality metric (BC) across the entire threshold range. Even when controlling for the node 413 degree by means of a partial correlation analysis, the positive association between PSS and BC remained 414 highly significant. This suggested that high PSS nodes are likely to contribute to the binding of information 415 across different sources in the brain by creating shortest paths between node pairs. Conversely, a strong 416 negative correlation was observed between PSS and local efficiency (Eff), and indicates that nodes 417 with a high PSS are unlikely to participate in strongly integrated local networks. To further explore the 418 association between the PSS measure and functional integration, we conducted a modularity analysis and 419 420 computed the participation coefficient (PC) of network nodes. A strong positive correlation between PC421 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.

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

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

442 Finally, we note that the nodal PSS does not merely recapitulate the betweenness-centrality metric. Although the correlation between PSS and BC measures was significant at all thresholds under study in 443 the binary networks analyses, only 4 of the 14 highest ranking PSS nodes overlap with the hubs identified 444 on the BC metric (Fig. 6). This may be explained by the fact that some nodes ranking highly on the 445 446 betweenness-centrality metric concurrently participate in strongly connected neighborhood clusters; their respective edges would thus form clique complexes at an early stage in the filtration, leading to low PSS 447 value. Moreover, the value of the correlation between PSS and BC was around R = 0.4 in both the 448 binarized and weighted network analyses, which further suggests that the PSS and BC do not reflect 449 450 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 DCmetric in this study, has previously been shown to engage in distributed networks thought to support mental 459 460 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

We also paid attention to the special case of high-ranking PSS nodes which did not qualify as "hubs" 463 on any of the three standard topological centrality measures (DC, Eff, BC). This subset of nodes was 464 anatomically restricted to the lateral frontal and parietal cortices. They included the middle and superior 465 frontal gyri, as well as inferior and superior sections of parietal gyri. These findings would suggest that, 466 relative to standard topological centrality metrics, the PSS may be particularly sensitive to the network 467 activity of frontal and parietal association areas located on the lateral surface of the brain. This would be 468 consistent with the established role of these regions towards supporting high-level cognitive and behavioral 469 functions requiring the large-scale coordination of network elements. The relative importance of PSS-hubs 470 471 towards the information processing capacities of the brain should notably be assessed in future studies by means of virtual lesions in whole-brain computational models [13, 14, 42]. 472 473

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 integration of information. The exact identities of these regions and the optimal experimental approaches 477 478 for identifying them remain unclear. However recent evidence would suggest that integrative nodes, such as those potentially identified via the persistence homological scaffold, require metastability for maximal 479 exploration of the full dynamic repertoire of the brain [22]. Previous research has employed diffusion tensor 480 481 imaging (DTI) and graph theoretical analysis to identify a subset of hubs which forms a central core or "rich-club" that has been suggested to be important for global brain integration by linking together spatially 482 remote network communities [41]. Yet, the mapping of a structural network architecture that can plausibly 483 484 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 homologogical scaffold may be particularly487 valuable in this regard.

488

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

498

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

514

515 Another limitation of this study, as mentioned in section 2.2.6, is the choice of the representative cycles for homology classes, which could result in selecting edges that do not belong to the shortest cycle around 516 a certain hole. A possible way around this limitation would be to perform an *a posteriori* analysis of 517 the cycles, in which one controls for the evolution of the subgraph's transitivity (as done in [31]). One 518 could also consider employing computationally cumbersome techniques to track the shortest path across 519 the filtration and then update the scaffold accordingly [16, 15]. Further work is needed to establish which 520 protocol would be most suited to the specfic case of fMRI networks. Our results on network communities 521 522 nevertheless suggest that the cycle choice issues might not be so critical in our study and potentially lead to a stronger PSS interpretation. Indeed network communities, being densely connected internally and strong 523 information integrators, likely constitute the network regions where connected triangle components reside 524 and thus the regions where different representative cycle choices are possible. Moreover, scaffold hubs 525 already tend to have large participation coefficients suggesting that they behave as information brokers 526 between these communities and are therefore, although imperfectly, capturing the large-scale homological 527 528 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. The computation of a local graph measure on the persistence homological scaffolds (PSS) differs from 531 standard applications of graph theory to functional neuroimaging data as the scaffolds are not derived 532 from typical dyadic interactions between network elements, and consider information from all edges in 533 the network. The results suggest that topologically central nodes in the persistence scaffold may play 534 important roles towards supporting the functional integration of information across brain modules. Future 535 work should investigate the sensitivity of the homological scaffolds and derived measures to disease-related 536 537 changes in brain function as well as the specific type of integration performed by the strongest edges and nodes in the scaffolds. 538

DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

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

AUTHOR CONTRIBUTIONS

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
fMRI data. P.E., G.P., F.V. developed and implemented the persistence homological scaffolds methodology
essential to this study. L-D.L., H.M.F. performed the graph theoretical analysis of the data. P.E., L-D.L.,
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
section. L-D.L. and P.E. wrote the introduction and discussion sections, with editorial guidance from
M.L.K., F.E.T. and G.D.

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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 $\langle abcf \rangle$ and $\langle cdef \rangle$. **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.

