

Pilot Study of Distinct Graphs Models in Analysis of Brain Aging in Resting-State Functional Connectivity Networks

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Abstract: Graphs have been used successfully to represent and analyze brain networks for many decades. Such structural and functional studies are important for revealing interactions between distinct areas of the brain that, for example, are associated with the performance of a specific task or the onset of a cognitive disorder like dementia. In this pilot study, resting-state functional magnetic resonance imaging data were acquired in a sex-balanced sample of 10 young (20.1 ± 2.1 years) and 10 old (65.6 ± 0.4 years), presumed healthy, adults. We examined the effects of age on whole-brain resting-state functional connectivity (RSFC) networks. We examined two main graph modeling approaches to analyze RSFC networks. These approaches employ different strategies or graph models for thresholding over the complete network or examining changes in graph density. We computed and compared one graph metric, the modularity, that was derived from the RSFC network graph models. Considering the need for a model that must preserve the network's connectivity, strategies that use spanning trees as seeds to gradually increase the graph's density seem more appropriate to represent brain networks.


1 INTRODUCTION


Neuroimaging techniques have become more accessible and frequently used in recent years and have facilitate the emergence of human brain studies, including investigations of brain aging. Such aging studies attempt to understand how the healthy brain transforms morphologically or functionally across the lifespan. Considering that in many countries people are living longer, it is important to first study healthy aging if we are to then attempt to understand pathological aging. This knowledge can then help understand and mitigate impacts of illnesses like cognitive loss and dementia. Functional magnetic resonance imaging (fMRI) is a widely employed, non-invasive method to investigate functional organization of and organizational change in the brain during aging. Resting-state fMRI (rs-fMRI) methods process the spontaneous fluctuations in the blood oxygen levels (or the

BOLD signal - *blood oxygen level-dependent*) that occur even in the absence of a stimulus or activation task (Lv et al., 2018).

To describe the brain functional organization, *i.e.*, its underlying functional connectivity, studies have modeled the brain as a highly structured network, known as the connectome (Hrybouski et al., 2021). Graph theory approaches naturally arise as a method for representing human brain networks. In the mathematical sense, a graph G is an ordered pair $G = (V, E)$ defined by a set of nodes (or vertices) V and set of edges (or links) E connecting the nodes (Chung, 2019). The use of graphs to represent networks is important as it enables characterization and analysis of brain functional organization using a variety of graph metrics.

This initial study aims to explore the computation of modularity graph metric according to distinct graph models (GMs). Such metric characterize relevant aspect of resting-state functional connectivity (RSFC) networks. We conducted an experiment using four

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GMs, corresponding to representations for RSFC networks, widely reported in the literature. This work makes contributions in the following areas:

- We present an up-to-date review of the literature of GM representations of the RSFC networks.
- We analyzed RSFC networks using a graph metric calculated for different GMs in order to improve understanding of the potential and limitations of each model.

The remainder of this paper is organized as follows: In Section 2 the literature survey protocol is presented. We then summarize our findings regarding the graph representation used to model RSFC networks. Section 3 describes our experiment methodology, expanding on the important details required to build distinct GMs. Section 4 summarizes our results and discusses the broader implications of our findings. Finally, Section 5 concludes the paper with final remarks and a discussion of remaining issues.

2 LITERATURE REVIEW

In this section we explain how we identify key works in the peer-reviewed literature on RSFC brain networks of healthy individuals.

We used the three-staged methodology in order to select relevant papers that explored graph theory, i.e., uses GMs to characterize and analyze RSFC networks in aging (Figure 1).



Figure 1: Three-stage protocol to select papers dealing with the representation of RSFC networks through graph models.

The paper extraction intended to answer the following questions:

1. What are the main graph approaches used to represent RSFC networks?
2. Concerning the identified approaches, what are the strategies or variations regarding to the graph models?
3. What other graph properties (or graph types) are important in characterizing RSFC networks?

2.1 Exploring Existing Reviews

In this stage we collect three recent review or systematic review papers, listed in Table 1, that works with

graph theory to characterize and analyze RSFC networks in aging.

The three review and systematic review papers identified a number of broad-based studies focused on brain aging in healthy individuals that analyzed RSFC networks. Combined, they cited a total of twenty-six papers that specified modeling of RSFC networks using graph theory. Only paper that explicitly mentioned using graph metrics were included. We excluded reports that focused on addressing specific diseases, trauma or that studied the effects of medications, other treatments or therapies. We also excluded reports not written in English. Twenty-five of these papers were selected (see list in Table 2) and one article was excluded (one study obtained rs-fMRI data in hypercapnia (Hou et al., 2019)).

2.2 Supplementary Screening and Inclusion/Exclusion Criteria

Because the most recent of the three review and systematic review examined papers published before June 2021 (Deery et al., 2023), a supplementary search was conducted, according to a three-step protocol as described in (Kitchenham, 2004), in order to include articles between June 2021 and June 2024.

The supplementary search was performed using two complementary databases: 1) IEEE Xplore¹ (engineering and computer science literature) and 2) PubMed² (biomedicine literature) using the research query: “(aging) AND (brain) AND (network) AND (functional connectivity) AND (review OR systematic review)”. The inclusion criteria initially considered only papers focusing on brain aging evaluated with RSFC networks analysis.

We used the same inclusion and exclusion criteria applied in previous stage. Finally, we have identified an additional six papers published after May 2021.

2.3 Studies: Identification and Summary

These 31 selected articles, including both stages, cover a period between 2007 and 2024, and constitute our source of primary studies. Those papers were analyzed in detail, specifically examining the GM used.

After analysis, we have classified each approach concerning the use of graph theory on three types of graph (GT - Graph Type) and four types of graph model (GM) (see Table 2). The GTs were:

¹<https://ieeexplore.ieee.org/Xplore/home.jsp>

²<https://pubmed.ncbi.nlm.nih.gov/>

Table 1: Review and systematic review papers selected on stage 1.

Year	Paper Title	Ref
2023	The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging	(Deery et al., 2023)
2021	Resting-state networks in the course of aging-differential insights from studies across the lifespan vs. amongst the old	(Jockwitz and Caspers, 2021)
2020	Functional brain connectivity changes across the human life span: From fetal development to old age	(Edde et al., 2020)

Table 2: Summary of graph based methods, summarizing study design, graph type (GT) and graph model (GM). Publications extracted from Ref (Deery et al., 2023),(Jockwitz and Caspers, 2021), and (Edde et al., 2020), and updated to June 2024.

Ref	Study Design	GT			GM			
		1	2	3	1	2	3	4
(Hrybouski et al., 2021)	CS	✓	✓	-	-	-	-	✓
(Grady et al., 2016)	CS	-	-	✓	-	-	✓	-
(Geerligs et al., 2015)	CS	✓	-	✓	-	-	✓	-
(Gallen et al., 2016)	CS	✓	-	-	✓	-	-	-
(Iordan et al., 2018)	CS	✓	✓	-	-	-	✓	-
(Betz et al., 2014)	CS	-	-	✓	-	-	-	✓
(Chan et al., 2014)	CS	-	✓	-	-	-	-	✓
(Stumme et al., 2020)	CS	-	-	✓	-	-	✓	-
(Alcauter et al., 2015)	CS	-	✓	-	✓	-	-	-
(Asis-Cruz et al., 2015)	CS	✓	✓	-	✓	-	-	-
(Marek et al., 2015)	CS	-	-	✓	-	-	✓	-
(Song et al., 2014)	CS	✓	-	✓	-	✓	-	-
(Thomason et al., 2014)	CS	-	-	✓	-	-	-	✓
(van den Heuvel et al., 2018)	CS	-	✓	-	✓	-	-	-
(Varangis et al., 2019)	CS	-	-	✓	✓	-	-	-
(Bagarinao et al., 2019)	CS	✓	-	-	✓	-	-	-
(Cao et al., 2014)	CS	-	✓	-	-	-	✓	-
(Li et al., 2016)	CS	✓	-	-	-	-	✓	-
(Onoda and Yamaguchi, 2013)	CS	-	-	-	-	-	-	✓
(Sala-Llonch et al., 2014)	CS	✓	-	✓	-	-	✓	-
(Meunier et al., 2009)	CS	✓	-	-	-	-	✓	-
(Achard and Bullmore, 2007)	CS	✓	-	-	-	-	✓	-
(Lehmann et al., 2021)*	CS	✓	-	-	✓	-	-	-
(Foo et al., 2021)*	CS	-	✓	-	-	-	-	✓
(Wang et al., 2024)*	CS	✓	-	-	-	-	✓	-
(Moretto et al., 2022)*	CS	-	-	✓	-	-	✓	-
(Filippi et al., 2023)*	CS	-	✓	-	-	-	-	-
(Chong et al., 2019)	CS/L	-	✓	-	-	-	✓	-
(Wen et al., 2019)	L	-	✓	-	-	-	✓	-
(Xiao et al., 2016)	L	✓	-	-	✓	-	-	-
(Pedersen et al., 2021)*	L	-	✓	-	-	-	-	✓

* = Additional paper identified in *supplementary screening*

GTs were: GT1-binary graph, GT2-weighted graph, only positive values, and GT3-weighted graph, positive and negative values.

GMs were: GM1-thresholding operation approach, GM2-spanning tree initial seed approach, GM3-density approach, and GM4-entire graph.

CS = Cross-Sectional; L = Longitudinal

GT1) binary graph (14/31, 45.2%), GT2) weighted graph, only positive values (12/31, 38.7%), and GT3) weighted graph, positive and negative values (10/31, 32.2%). Some papers work with multiple GT, which can result in a sum greater than 30. The use of binary graphs was associated with the evaluation of aspects of the network topology. This observation is related to the scope of the study, *i.e.*, being able to evaluate only aspects of the network topology, as in the case of using binary graphs, or when it was necessary to evaluate more specific graph properties, such as strength and shortest path length. The detailed review also identified an alternative GM aimed at investigating brain hubs, *i.e.*, highly connected regions of the neurocognitive functional networks (Filippi et al., 2023). This approach was recently used to obtain new adjacency matrices from the analysis of the distance of any brain region, according to the degree of step-wise connectivity and the seed area (*i.e.*, hubs).

The models included GM1) based on a thresholding operation (fixed value or range) (8/31, 25.8%), GM2) based on the construction of a spanning tree and the addition of successive edges (1/31, 3.2%), GM3) based on the pre-defined values of graph density range (14/31, 45.2%), and GM4) based on the entire and non-sparse graph (7/31, 22.6%).

The first model (GM1) used thresholding. One of the main challenges in applying strategies that use a thresholding process is defining the threshold itself, as this operation may include irrelevant or disregard relevant information from the RSFC network (van den Heuvel et al., 2017). One way to mitigate the impact of using a single threshold is to apply a range of values. Indeed, most studies use a threshold range (Asis-Cruz et al., 2015)(van den Heuvel et al., 2018) (Chong et al., 2019). In Bagarinao (Bagarinao et al., 2019), for example, a threshold range [0.20,0.40] was used. We also found studies that used a single threshold (Alcauter et al., 2015)(Xiao et al., 2016). One aspect that is not always explicitly reported was the fact that the thresholding process can generate disconnected RSFC networks. In this situation, the calculation of graph metrics were performed separately on either each connected component or only on the largest connected component.

GM2 derives a spanning tree (MST - minimum spanning tree in that case) as a seed and gradually include a percentage of edges, as adopted by (Song et al., 2014). This method represents an interesting approach as it guarantees the connectivity of the graph. One important point is that the weights of the edges added in a minimum spanning tree are those with smaller values, in ascending order, according to Kruskal's algorithm (Fornito et al., 2016). Consider-

ing the graph density approach added relevant edges, *i.e.*, stronger connections, in this case, therefore, it would be appropriate to work with a *maximum* spanning tree (MaxST).

GM3 consists of defining a range of graph density values (Grady et al., 2016) (Marek et al., 2015) and generating representations of the RSFC network. Graph density is a measure of the ratio between edges and nodes. The density is 0 for a graph without edges and 1 for a complete graph. The graph density strategy is similar to spanning trees because with the exception of not using a seed, it also consists of gradually adding relevant edges. One limitation is the possibility of creating disconnected graphs. We found papers that worked with graph densities that ranged between 1% and 60% (Grady et al., 2016) and 1% and 25% (Marek et al., 2015).

The final model (GM4) used the entire graph, such that each entry of the Pearson correlation matrix corresponds to an edge in the graph. In (Thomason et al., 2014), for instance, both positive and negative correlation values were used in order to build the equivalent graph. On the other hand, (Chan et al., 2014) only positive values of the correlation matrix were used.

Table 3 list the five most cited articles listed in Table 2. The most cited of these papers presented the calculation of local and global efficiency graph metrics, in addition to using a graph model approach based on graph density (Achard and Bullmore, 2007).

Table 3: Highly cited papers (Source: PubMed).

Ref	Total citations	Citations per year
(Achard and Bullmore, 2007)	1113	> 60
(Chan et al., 2014)	399	≈ 40
(Betzel et al., 2014)	392	≈ 40
(Geerligs et al., 2015)	348	≈ 40
(Meunier et al., 2009)	370	≈ 25

2.4 Considerations on Review Findings

The connectivity of a GM is an important feature in the analysis of RSFC networks. Graph metric computation may undergo changes according to the connectivity property, such as corresponding to the value of the largest connected component. Jordan *et al.* (Jordan et al., 2018), for instance, explicitly pointed out the number of nodes that were disconnected in the graphs built in his modeling. Meunier *et al.* (Meunier et al., 2009) defined the number of connections, in a range between 100 and 400 edges (or links), in order to keep the graph connected. An interesting strategy that guarantees the connectivity of a graph model is the use of minimum spanning trees (Song et al.,

2014). A spanning tree is a tree-like subgraph of a connected graph that includes all vertices. More consistent results may be found when employing a maximum spanning tree, instead minimum spanning tree, because the most relevant edges of the graph are added in sequence.

To correctly understand the brain aging process trajectory, it is necessary to explore longitudinal data. This methodology investigates changes in intra-individual functional connectivity networks and allows us to understand the compensatory changes carried out by the different RSFC networks in healthy individuals. Only a few studies (4/30, 13.3%) used longitudinal data when calculating graph metrics (Chong et al., 2019)(Wen et al., 2019)(Xiao et al., 2016)(Pedersen et al., 2021). These four studies only examined one age group and, therefore, have limitations in terms of extrapolation of results over the adult life span.

Choosing a GM is not just a question of efficiency, as they all enable RSFC network characterization using graph metrics via appropriate parameter definition. Choosing a GM is about knowing the conditions for acquiring and processing rs-fMRI data and the study sample, avoiding spurious connections and biases (Rubinov and Sporns, 2010)(Varangis et al., 2019).

We also observed the existence of distinct nomenclatures to represent the number or percentage of edges in the graph model, as well as in the definition of relevant entries (correlation values) of the FC matrix. Considering that the origin of the term *thresholding* is related to the modification of intensity or amplitude values in a matrix, we propose to use the simple terminology for the GMs found in the literature. The described GMs and graph analysis scenarios can be organized into two major approaches for analyzing RSFC networks: 1) *Thresholding*, where the weighted edges of the corresponding graph must be greater than a value or a range of values, and 2) *Graph density*, where the resulting graph is constructed from a percentage of connections in the original network, including the entire graph.

3 METHODS

The modularity analysis pipeline is shown in Fig. 2 and consisted of four main steps described in this section.

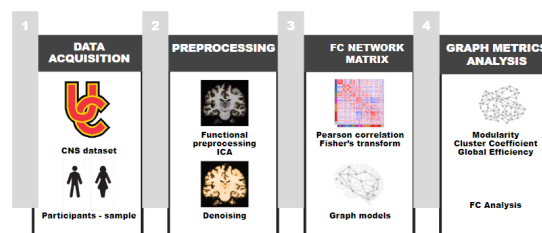


Figure 2: Overview of processing pipeline.

3.1 Data Acquisition

MR imaging data in this study were acquired as part of the Calgary Normative Study (CNS) (McCreary et al., 2020). The CNS is an ongoing longitudinal study, started in 2013, that focuses on collecting quantitative data from community dwelling, presumed healthy adults (18-90+ years). Several types of MR neuroimaging were performed in the CNS including rs-fMRI. To pilot our methods, we examined twenty (20) individuals extracted from the CNS database, ten (10) from a young and ten (10) from an older group. Table 4 lists the demographics of the groups.

Table 4: Dataset sample demographics.

Group (Number)	Sex Ratio	Age (years)
Young ($N = 10$)	50% Female 50% Male	20.1 ± 2.1
Old ($N = 10$)	50% Female 50% Male	65.6 ± 0.4

3.2 Image Preprocessing

The preprocessing pipeline consists of the preparation and analysis of the rs-fMRI images. The pipeline comprises several key steps: 1) skull stripping using BET, 2) motion correction using MCFLIRT (Motion Correction FMRIB Linear Image Registration Tool), 3) interleaved slice-time correction, 4) spatial smoothing, 5) temporal high-pass filtering, 6) independent component analysis (ICA) and 7) functional-structural registration. Details of the pipeline are described in (Sidhu, 2023).

3.3 FC Network Matrices and Graph Models

From the average BOLD time series, a FC matrix of size 200×200 was derived for each individual by calculating the Pearson correlation (r) across the time series (Sidhu, 2023). This matrix size was obtained

from the brain segmentation into 200 anatomical regions using the Schaefer-Yeo atlas. We consider a brain organization based on the existence of seven relevant modules (Sidhu, 2023): Visual network, Sensorimotor network, Frontoparietal network, Dorsal attention network, Limbic network, Ventral attention network, Default mode network. After analyzing the quality of the rs-fMRI data, FC matrix entries from the left and right limbic networks were excluded because of signal loss resulting from MR susceptibility artifacts. Fisher's r -to- z transformation was then applied to the Pearson correlation values and the main diagonal of the FC matrix was set to zero to exclude self connections.

We explored four GMs that can be used to represent RSFC networks from FC matrices. These GM were first identified in our systematic review (Table 2):

- **GM 1: Thresholding** applied a threshold range directly to the Pearson correlation matrix.
- **GM 2: Minimum Spanning Tree** was built from all graphs. Graph connectivity was preserved and edges were added according to their weight, choosing first to add those with the lower values.
- **GM 3: Graph Density** used a range of values for the graph density metric. We gradually add edges (as a percentage) to the model graph, as in the previous model.
- **GM4: Entire Graph** used all positive values of the Pearson correlation matrix. Each matrix entry corresponds to an edge of the graph.

We decided to include a fifth GM, **GM5**, corresponding to a variation of spanning tree called **Maximum Spanning Tree**. Unlike the Minimum spanning tree, this tree is built by considering the strongest connections, as done by the thresholding and graph density approaches. In that case, edges are added according to their weight, choosing first to add those with the higher values. In all cases where a range was used, the final value of the graph metric was the average value calculated over that range.

3.4 Modularity: Graph Metric

Modularity (Q) measures the relative strength of a network division into groups. Modularity reflects the existence of subnetworks within the full network.

$$Q = \sum_{I \in M} \left[l_{II} - \left(\sum_{J \in M} l_{IJ} \right)^2 \right] \quad (1)$$

where the network is divided into a set of nonoverlapping modules M and l_{IJ} is the ratio of all links that

connect nodes in module I with module J . RSFC networks with high modularity have dense connections between nodes within the module but sparse connections between nodes across different modules. Details concerning modularity can be found at (Fornito et al., 2016).

4 RESULTS AND DISCUSSIONS

Our objective was to highlight trends in the five GMs between the young and old age groups and compare them with literature findings. For all experiments, we use Python and the networkX library (<https://networkx.org/>).

The GMs examined were (section 3.3): GM1 – thresholding with fifteen steps in the range $[0.05, 0.4]$; GM2 and GM5 – minimum and maximum spanning trees followed by a gradual addition of edges in the range of 2% and 40% (Song et al., 2014); GM3 – graph density using the range $[1\%, 25\%]$; and GM4 – entire graph (Marek et al., 2015). For all models, we processed only positive Pearson coefficient values and computed the modularity (section 3.4) to evaluate age-related change in the GMs. Figure 3 presents results for all examined GMs.

As we can see in Figure 3, Q decreased in the old compared to the young group, over a range of different thresholds and edges densities. This was also observed in GM4, where the mean values obtained for the young and old groups were 0.1162 and 0.1099, respectively. This finding is similar to that obtained in Deery (Deery et al., 2023) who found that in 100% of studies Q decreased with age.

In the neuroimaging field, the construction of networks and their analyses draws on the concept of small world networks (Deery et al., 2023). Small-world networks are defined as networks that are significantly more clustered than random networks (Rubinov and Sporns, 2010). Except for the GM4 model, all GMs presents mean modularity values greater than 0.3, an indicative of nonrandom community structure, i.e., the existence of modular structure of functional brain networks across the adult lifespan (Song et al., 2014). Finally, Minimum and Maximum spanning trees (GM2 and GM5, respectively) present a similar behavior; however, considering that GM5 includes first the most relevant connections in terms of Pearson correlation values, this would be the most coherent choice.

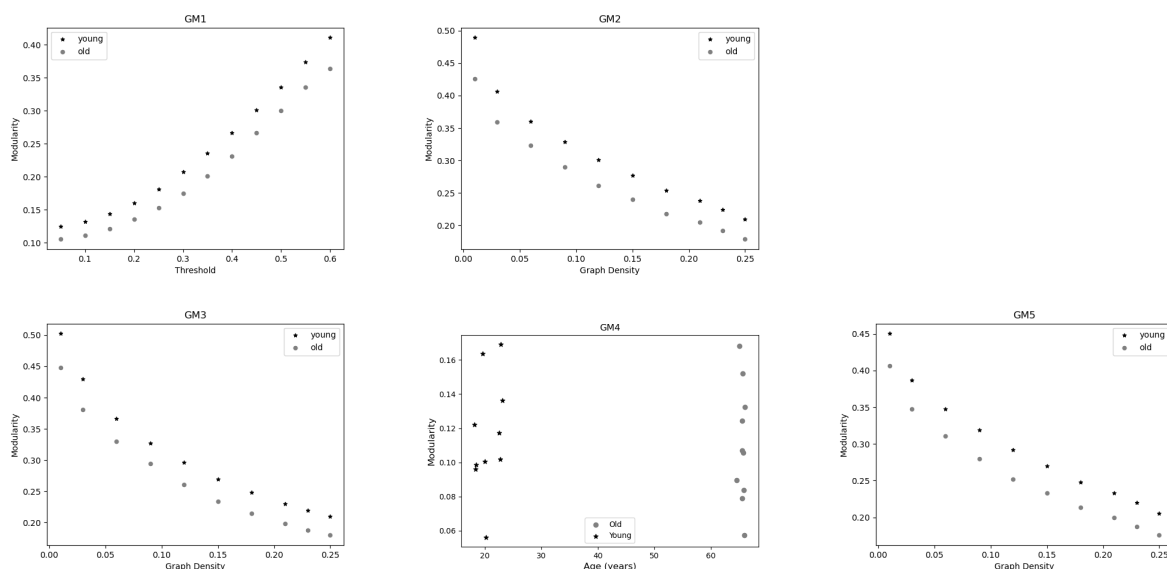


Figure 3: Modularity values by graph model. for young (black stars) and old individuals (gray circles). Rows are graph models: GM1, GM2, and GM3, GM4 and GM5 (top to bottom).

5 CONCLUSIONS

We found thirty peer-reviewed papers that addressed changes in RSFC networks in aging using graphs (Table 2). Many additional papers used graphs to study diseases and disorders, but were outside our selection criteria. It was possible to identify two approaches to model brain as graphs: Thresholding operations (that act on the Pearson correlation values), and approaches that use a gradual increase in graph density (that act on the number of edges or links). More studies only worked with positive Pearson correlation values, than those using positive and negative values. In addition, binary graphs were widely used to express network characteristics, such as modularity and clustering coefficient. Also of note is the maintenance of the graph connectivity property, observed from its adjacency matrix. Graph connectivity is important because it allows the application of other mathematical approaches and more advanced computational techniques. In this context, the model that uses spanning trees naturally results in connected graphs.

We carried out a pilot experiment that compared a common graph metric (modularity), computed over distinct graph models representing RSFC networks, to analyze existing differences among groups of young and old healthy individuals. This experiment presents findings similar to those obtained in the literature, which indicate that the value of modularity decreases with aging. We highlight that this work consists of an exploratory analysis of GMs. An

in-depth study of the full CNS dataset with respect to brain aging including other parameters is warranted. Finally, to understand the brain aging process from a different perspective, we should examine longitudinal data, that is, study changes in intra-individual functional connectivity networks, considering age as a continuous variable. This type of study will also allow us to understand changes made in different RSFC networks over age in healthy individuals.

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