Altered Connectedness of the Brain Chronnectome During the Progression to Alzheimer’s Disease

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Accepted: 3 November 2021 / Published online: 26 November 2021
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Abstract
Graph theory has been extensively used to investigate brain network topology and its changes in disease cohorts. However, many graph theoretic analysis-based brain network studies focused on the shortest paths or, more generally, cost-efficiency. In this work, we use two new concepts, connectedness and 2-connectedness, to measure different global properties compared to the previously widely adopted ones. We apply them to unravel interesting characteristics in the brain, such as redundancy design and further conduct a time-varying brain functional network analysis for characterizing the progression of Alzheimer’s disease (AD). Specifically, we define different connectedness and 2-connectedness states and evaluate their dynamics in AD and its preclinical stage, mild cognitive impairment (MCI), compared to the normal controls (NC). Results indicate that, compared to MCI and NC, brain networks of AD tend to be more frequently connected at a sparse level. For MCI, we found that their brains are more likely to be 2-connected in the minimal connected state as well indicating increasing redundancy in brain connectivity. Such a redundant design could ensure maintained connectedness of the MCI’s brain network in the case that pathological damages break down any link or silenced any node, making it possible to preserve cognitive abilities. Our study suggests that the redundancy in the brain functional chronnectome could be altered in the preclinical stage of AD. The findings can be successfully replicated in a retest study and with an independent MCI dataset. Characterizing redundancy design in the brain chronnectome using connectedness and 2-connectedness analysis provides a unique viewpoint for understanding disease affected brain networks.

Keywords Graph theory · Dynamic functional connectivity · Alzheimer’s disease · Mild cognitive impairment

Introduction
The human brain can be modeled as a complex network or graph based on various connectivity metrics, such as functional connectivity (FC, denoting edge weights) that is interpreted as interactions or coordination among different brain regions (denoting nodes) (Sporns, 2013). There have been various means to construct brain functional connectome, such as Pearson’s correlation of the resting-state fMRI (rs-fMRI) signals, and it has been recently extended to time-varying (non-stationary or dynamic) connectome, or chronnectome (Chang & Glover, 2010; Cribben et al., 2012; Hutchison et al., 2013; Lindquist et al., 2014; Musso et al., 2010; Sakoğlu et al., 2010; Yuan et al., 2012). The FC or dynamic FC serve as sensitive non-invasive measurements to understand disease-related network alterations. Alzheimer’s Disease (AD) is generally regarded as a disconnection syndrome (Dai et al., 2019) with gradual network topological changes in a prolonged period with a concealed onset (Adeli
et al., 2005a, b; Romero-Garcia et al., 2016). Many recent efforts have been put forth to understand the neural underpinning of AD in its early, preclinical stage, also known as mild cognitive impairment (MCI) (Binnewijzend et al., 2012; Gauthier et al., 2006; Misra et al., 2009; Petersen et al., 2001a; Schwab et al., 2018), with brain network modeling using graph theory (Hojjati et al., 2017).

Most complex brain network studies on the AD-related alterations have been largely based on characteristic path length (i.e., the shortest paths) and its derivatives (e.g., assortativeness and resilience) (Achard et al., 2006; Kasthuriratna et al., 2013; Newman, 2002, 2006; Ravasz & Barabási, 2003). For example, the averaged characteristic path length of all pairs of brain regions characterizes network’s global efficiency, while the shortest path-based local connectedness defines local clustering coefficients or local efficiency. Recent studies also broadly define small-worldness, an important brain network property balancing local integration and global reachability (Stam et al., 2006). AD has been usually associated with disconnected or less efficient connections with suboptimal organization (Dennis & Thompson, 2014; Prasad et al., 2015; Supekar et al., 2008; Zippo et al., 2015). MCI, on the other hand, usually manifests increasing FC and suboptimal small-worldness (Yao et al., 2010, 2018; Zhou et al., 2011), possibly due to a compensatory effect for maintaining normative cognition. While these studies jointly indicated that cost efficiency can be a good property of the brain network where brain regions are optimally connected to work efficiently together, this phenomenon can be also prominent when only network’s backbone (e.g., the top 5% strongest connections) considered (Latora & Marchiori, 2001; Ma et al., 2018). The brain network’s topology can manifest different properties when viewed with more redundant (but weaker) links, which could be equally important as the efficiency-based metrics in understanding the neural mechanisms of diseases (Bullmore & Sporns, 2009; Wang et al., 2011, 2015).

In this paper, we investigated brain network changes during AD progression by using new brain network topological metrics that are different from the conventional cost-efficiency methods. We did not only rely on the shortest paths (Fig. 1a) but also the less investigated (Di Lanzo et al., 2012), alternative (or parallel, see a toy example in Fig. 1b) paths between each pair of nodes. For example, a magnetoencephalography (MEG)-based FC study defined various redundancy metrics at each frequency band and found that the brain functional network expresses more redundancy than the random network (Di Lanzo et al., 2012). They further calculated an average number of alternative paths in an electroencephalogram (EEG)-based FC network in the entire network of spinal cord injured patients as a global measurement of redundancy but did not find any significant changes compared to the healthy subjects (Fallani et al., 2011). In an AD vs. control study, education level was found to act as a cognitive reserve by strengthening the redundancy of a partial brain network constructed by using diffusion MRI (Yoo et al., 2015). The inclusion of redundant paths can imply different aspects to the brain connectome, which is further summarized as different types of efficiency, together describing trade-offs among efficiency, cost, and resilience (Avena-Koenigsberger et al., 2018). Such a redundancy design in other natural networks has been consistently found and studied (Corson, 2010; Härkegård & Glad, 2005; Steiglitz et al., 1969). Another paper also used redundancy definitions to explore brain functional network changes among different subjects and through time (Sadiq et al., 2021). The previously well adopted metrics such as global efficiency was defined based on the shortest path length in the network, which just takes care of the minimum length between any pair of the nodes; the redundant connections instead pay attention to the number of available connections, including the shortest path and other longer paths that were not as important as the shortest path in the definition of global efficiency. The availability of multiple connections provides more information about what will happen to the network if some of the nodes or links are removed or damaged. This is the most important difference that one can obtain from the redundancy measurements compared to other metrics in the network such as weighted degree, clustering coefficient, global efficiency and modularity. In this study, we analyzed much denser brain networks by also including weak edges, where the backup routes will likely emerge, and the redundancy could become the dominant theme compared to cost efficiency. Different from these previous studies, we proposed an intuitive and easy-to-calculate metric describing whether there are always other paths in addition to the shortest path for every pair of nodes. This might illustrate more details about the robustness of connections between pair of nodes.
Theoretically, a network $G$ with an edge set $E(G)$ and a node set $V(G)$ is connected if there exists a path for any two nodes $a,b \in V(G)$. A connected network $G$ is $2$-connected if for every two nodes $a,b \in V(G)$, there are at least two paths between $a$ and $b$ (with this feature that these paths have no nodes in common except $a$ and $b$). From the graph theory point of view, we can see that because of the existence of at least two paths between every pair of nodes $a,b \in V(G)$, by removing every single node, there is still a connection between $a$ and $b$. So, there is no node that by removing it from the network, the remaining network will not be connected. In other words, in a $2$-connected network $G$, for every node $x \in V(G)$, $G \setminus x$ is connected ($\setminus$ denotes the removal of a node and all the edges adjacent to it). Taking all these together, although a $2$-connected network has the feature of the connected network, but also has better robustness with a merit of the redundancy design (a cycle consisting of any two nodes) compared to the connected network no matter where the damage occurs. By increasing network density, brain network will change from disconnected to connected and then to $2$-connected. Thus, two critical points may exist during such a transition: the density that a network first becomes connected from disconnected and the density when it transits from connected to $2$-connected. $2$-connected network has a good property that, if any shortcut or node is removed, all the remaining regions are still connected (Fig. 1a, b). Of note, if multiple paths exist between $a$ and $b$ but all of them share the same node $c$ (Fig. 1d), they are not redundant paths, and the network is not $2$-connected. Again, this is not a resilient network because any damage on the node $c$ will break the network. From Fig. 1, it is easy to know that the $2$-connectedness of a network can provide a sensitive measurement of AD-related changes as a tiny rewiring to the network could dramatically change its $2$-connectedness.

Since AD progression is a spectrum with gradual changes starting from NC converting to MCI, characterizing connectedness and $2$-connectedness of the brain FC networks at different stages could better help to understand how AD progression impacts the brain. Due to the findings that the brain FC network changes its topology to meet the moment-to-moment requirement for adaptive thinking and other high-order cognitive functions (e.g., attention and alertness) (Damaraju et al., 2014; Demirtas et al., 2016; Hutchison et al., 2013; Marusak et al., 2017), we further assumed that the brain could be connected at different density levels in different period of time. Thus, we analyzed connectedness, $2$-connectedness and their changes in brain dynamic FC networks. Specifically, we separately assessed connectedness and $2$-connectedness of the time-varying FC networks with varied network densities to reveal the aforementioned critical points in a time-resolved manner in NC, MCI, and AD, with specific focuses on both the transitions from disconnected to connected states and those from connected to $2$-connected states, and vice versa. Since AD is considered as a disconnected syndrome, we hypothesized that the connectedness status has been altered in AD versus NC and that the brain connectome in MCI might generally have more frequently increased redundancy as a compensatory effect to maintain normative cognitive abilities.

**Methods**

**Data**

In this study, we apply our method to the Alzheimer’s Disease Neuroimaging Initiative (ADNI) datas (http://adni.loni.usc.edu/). Launched in 2003, the original goal of ADNI was to define imaging biomarkers for use in clinical trials of AD. The current goal has been extended to discover more effective methods to detect AD earlier at its pre-dementia stage. Data quality control was carefully conducted in the ADNI projects to make sure all the data from different imaging centers have the same imaging quality (Jack et al., 2008) (e. g., same imaging protocol, same scanner, and comparable signal-to-noise ratio). The 7-min rs-fMRI data (140 volumes) was processed using AFNI (Cox, 1996) according to a standard pipeline (Yan & Zang, 2010). Specifically, the first ten volumes are discarded, followed by a rigid-body head motion correction and a nonlinear spatial registration to the Montreal Neurological Institutes (MNI) space. Frame-wise displacement (FD $>0.5$) was considered as excessive head motion and the subjects with more than $2.5$-min data (50 volumes) labeled as excessive head motion were discarded (Power et al., 2014). FC was assessed using a functional brain atlas (Shen et al., 2013) consisting of 268 nodes covering the entire brain. Mean rs-fMRI time series of each brain region was band-pass filtered (0.015–0.15 Hz) and further processed to reduce artifacts by regression analysis (nuisance regressors include head motion parameters (the “Friston-24” model), the mean BOLD signal of the white matter, and that of the cerebrospinal fluid).

In the first run of analysis, we compared the dynamic properties of connectedness and $2$-connectedness between NC, MCI and AD subjects as a main study to understand how dynamic brain functional network changes its redundancy during AD progression. The subjects were selected from ADNI-Go and ADNI-2 only including the baseline scans and ensuring age ($p=0.752$, one-way Analysis of Variance (ANOVA), Table 1) and gender matched among all three groups. Due to the limited sample size of ADs, we selected the same amount of NC and MCI subjects to make sure as many matched data as possible were used.

**Overview of the Dynamic Connectedness and 2-Connectedness Analysis**

All the analyses were implemented in MATLAB 2017b (2017), SAGE 8.6, Python 2.7, and SPSS 23. Our method includes
the following steps for every subject. The flowchart is shown in Fig. 2. For each subject, we used a sliding window of 60 s (1 min, or 20 TRs, as suggested by the previous dynamic FC studies (Leonardi & Ville, 2015)) and a step size of 3 s (1 TR, as also used in the previous studies), there would be an overlap of 57 s between every two consecutive sliding windows. By using a sliding window method, we could generate many brain networks along time, thus characterizing dynamic FC. For the BOLD rs-fMRI signals within each window, pairwise Pearson’s correlation was used to calculate brain FC between every pair of the 268 nodes (Fig. 2a). For each of the time-varying FC networks, we calculated its connected and 2-connected properties at each density level, resulting in a connectedness and 2-connectedness property time series for each subject. To do this, by definition, connectedness and 2-connectedness are derived from binary networks, where network density is an important parameter that will affect such properties. With a lower density (fewer edges), a network is less likely to be connected, and vice versa. Searching for a critical point of network density around which the network changes its connectedness and 2-connectedness are essential for sensitive group comparisons and for avoiding network saturation at both ends of densities. We applied $H$ different density thresholds to each weighted dynamic FC network to generate $H$ binary networks in each of the $T$ sliding windows (Fig. 2b). Specifically, steps (a) and (b) of Fig. 2 are the same as many previous dynamic network construction and multiple threshold-based binary network analysis methods. In the next step, Fig. 2c, network connectedness (the sparsest network with no node singled out) is investigated, and the corresponding sparsity is considered as a connectedness state. For example, if a network at time $t = 1$ with 10% Table 1 Demographic characteristics (Mean ± SD) of NC, MCI, AD (used in the main analysis) as well as EMCI and LMCI subjects (also included in the validation analysis)

| Gender | (Male/Female) | age (year) | MMSe |
|--------|---------------|------------|------|
| NC     | 49 (26 M, 23 F) | 73.1 ± 6.5 | 29.1 ± 0.9 |
| MCI    | 49 (26 M, 23 F) | 74.3 ± 9.8 | 27.9 ± 1.6 |
| AD     | 49 (26 M, 23 F) | 73.3 ± 8.5 | 23.1 ± 2.5 |
| EMCI   | 49 (26 M, 23 F) | 74.1 ± 7.6 | 28.2 ± 1.8 |
| LMCI   | 49 (26 M, 23 F) | 72.8 ± 7.7 | 26.1 ± 1.9 |

Fig. 2 The framework of the dynamic connectedness and 2-connectedness analysis. (a) Sliding window correlation-based dynamic FC analysis; (b) Constructing binary networks with different density levels for each sliding window-derived network; (c) Calculating a state vector for time-varying connectedness, a state vector in which each state represents the minimum density level for every time window that the network is connected (shown by blue points); (d) Calculating another state vector for time-varying 2-connectedness by re-visiting the previously detected connected states in step (c) to check whether they are 2-connected or not; (e) and (f) Calculating the transition matrix from the obtained connected and 2-connected state vectors from steps (c) and (d); and (g) Conducting group comparison analysis for each time-varying connectedness and 2-connectedness feature among NC, MCI and AD groups.
sparsity is the sparsest network that is connected (with no node singled out), then the connectedness state at \( t = 1 \) is 2; at time \( t = 2 \), this network can be connected at 5% sparsity, then the connectedness state at \( t = 2 \) is 1. Then, in the next step, Fig. 2d, we check if at a certain minimum density level, a connected network is also 2-connected or not. For example, as we can see in Fig. 2d, at \( t = 1 \), the network is connected but not 2-connected (i.e., by removing a certain node, the network will become not connected), so we define this state as state 1. At \( t = 2 \), the network is connected and 2-connected (i.e., no matter removing any node, the network is still connected), so we define this state as state 2. Next, utilizing two obtained state vectors for every subject, we calculated two transition probability matrices for each subject, the same as previous studies on brain dynamic states (Fig. 2e, f). By employing all obtained values from the transition probability matrices, we conducted statistical analysis comparing the redundancy metrics among the three groups (Fig. 2g). In this study, \( H = 19 \) (from 5 to 95% with a step size of 5%) and \( T = 111 \) (windows). Thus, for every sliding window of every subject, 19 binary networks were achieved.

Please be noted that the thresholding scheme, definition of brain states, and network robustness (or resilience) have all been used in the previous studies. The thresholding strategy previously widely used multiple density thresholds, minimal spanning tree, and even no threshold at all (which generates a weighted network). In this study, we set up multiple density thresholds to avoid arbitrary threshold settings with a single network density. The identification of brain states from a dynamic network in previous studies largely depends on data-driven algorithms such as clustering and similar global optimization methods, but this is not based on clustering in our study. We simply determine if a network is connected or not, across multiple present thresholds, based on which a k-state transition matrix is built (Fig. 2c–e); we also determine whether at certain minimal density a connected network is also 2-connected or not, based on which a 2-state transition matrix is build (Fig. 2d–f). Please note that the second type of state definitions are made for each subject across time (sliding windows), thus irrelevant to the network density levels. As for the network robustness definition, the previously widely used network resilience is indeed defined by attacking the hub regions and calculating the difference of network global efficiency (Cascone et al., 2021); this is however essentially similar to our network connectedness metrics. Instead of calculating global efficiency changes by removing hub regions, our network connectedness can be considered as a binarized version (whether the network is connected or not). We believe that this will increase the disease detection sensitivity and more intuitive from network neuroscience point of view.

### Characterizing Connectedness and 2-Connectedness States

After applying \( H \) density levels on \( T \) time windows \( H^*T \) binary networks were achieved. Denote these networks by \( G_{th} \), \( 1 \leq t \leq T \) and \( 1 \leq h \leq H \). In each window, let \( h \) be the minimum density that makes the corresponding network connected. With \( h > h_{cr} \), the networks will be all connected with more redundancy; with \( h < h_{cr} \), the networks are all disconnected. The connectedness and 2-connectedness were assessed at such critical points to avoid trivial results and sensitively detect disease-related alterations. Such critical points can be further regarded as “brain states” in terms of the connectedness (Fig. 2c) and 2-connectedness (Fig. 2d) at a certain period. Denote such a critical network by \( G^*_t \). Like the previous dynamic FC analysis that identifies certain “brain state” for a time window \( t \), we defined a connected state for \( G^*_t \) and assign \( h_t \ (1 \leq h_t \leq H) \) as its state label. For example, as shown in Fig. 2c, the network’s connectedness in \( t = 1 \) is in state \#2, or \( C_t = 2 \). We can create a connected state vector \( C = \{ C_t \} \ (1 \leq t \leq T) \) when concatenating the connected states in all time windows, indicating how the dynamic brain network changes its connectedness property. The definition of connected states inherently codes network topology across multiple density settings.

We further checked the \( G^*_t \) to see if it was also 2-connected. If so, we define the network as it is in a 2-connected state \#2; if not, state \#1. Likewise, we further created a 2-connected state vector \( B = \{ B_t \} \ (1 \leq t \leq T) \). For example, \( B_t = 1 \) (connected but not 2-connected) and \( B_t = 2 \) (both connected and 2-connected) (Fig. 2d). The state vector \( B \) describes how the time-varying brain FC network changes its 2-connected state along time.

There are 19 possible states (since \( H = 19 \)) for connectedness. However, we found that most transitions among the connected states occurred between \#1 to \#4; therefore, only the first four connected states were considered in the following analysis. Both of the 2-connected states were used. As the state of 2-connectedness was determined according to the critical point in terms of connectedness, it is irrelevant to a specific network density. Of note, one can define 2-connected states in the same way as that of the connected states; however, since connectedness is a necessary condition for a network to become 2-connected, further checking if the same critical points generates 2-connected network could reveal more sensitive information to subtle changes in the network topology.

### Transition Among Different Connectedness States and 2-Connectedness States

We further quantified the dynamic properties of the connectedness and 2-connectedness states with a transition matrix (describing the probability of one state transitioning to
another) and a steady state vector (describing the probability of a certain state be cumulatively occupied given a long enough time, which equals to the normalized “dwelling time”) based on Markov Chain (Chavez et al., 2010; Williams et al., 2018). This resulted in a $4 \times 4$ connectedness transition matrix $P^C := \{p^C_{ij}\}$ ($1 \leq i, j \leq 4$), where $p^C_{ij}$ indicates the probability of changing from state $i$ to $j$, and a $2 \times 2$, 2-connectedness transition matrix $P^B := \{p^B_{ij}\}$ ($1 \leq i, j \leq 2$). The steady state vector is a probability vector $S$ that satisfies the equation $S P = S$, where $P$ is the transition matrix. It was solved as the left eigenvector of $P$ corresponding to the eigenvalue of 1. $S^C$ and $S^B$ have a length of four and two, respectively. Therefore, we generated 26 different features, including 16 $P^C_{ij}$ in $P^C$ and \{$S^C_{11}, S^C_{12}, S^C_{21}, S^C_{22}, p^B_{11}, p^B_{12}, p^B_{21}, p^B_{22}, S^B_{11}, S^B_{12}\}$ for every subject. Please note that $p^B_{11}$ and $p^B_{12}$, $p^B_{21}$ and $p^B_{22}$, as well as $S^B_{11}$ and $S^B_{12}$ indicate the same features, because $p^B_{11} + p^B_{12} = 1$, $p^B_{21} + p^B_{22} = 1$, and $S^B_{11} + S^B_{12} = 1$. Therefore, only 23 independent features needed to be considered, containing 16 $P^C_{ij}$ in $P^C$ and \{$S^C_{11}, S^C_{12}, S^C_{21}, S^C_{22}, p^B_{11}, p^B_{12}, p^B_{21}, p^B_{22}, S^B_{11}, S^B_{12}, S^B_{11}, S^B_{12}\}$. However, for completeness, we considered all the 26 features in tables and figures in the following analysis.

### Statistical Comparisons Among NC, MCI, and AD

For each of the 26 dynamic connectedness features, we conducted a Kruskal–Wallis test (a non-parametric version of the one-way ANOVA) to detect group differences among NC, MCI, and AD groups. Family Wise Error (FWE) corrected $p < 0.05$ was used to indicate significant group differences. Mann–Whitney U-tests (a non-parametric version of the two-sample t-test, two tailed) was further used to conduct post hoc pairwise comparisons for the significant Kruskal–Wallis test results ($p < 0.05$, FWE corrected).

### Validation with Two Independent MCI Subgroups

To further validate the main results and to see if the revealed abnormalities can be detected at an even earlier stage of MCI, we conducted a second analysis by replacing the MCI group with an independent dataset consisting of two different age- and gender-matched MCI subgroups (early(E-) and late(L-) MCI (Edmonds et al., 2019) selected from the ADNI GO/2 (Table 1). Therefore, we had four different groups (NC, EMCI, LMCI, and AD) that allowed us to further reveal the gradual changes and earlier signs (as shown in the EMCI group) of the AD progression. The NC and AD groups are the same as those in the main analysis. The four groups have comparable age ($p = 0.872$, one-way ANOVA) and with gender matched. All the data analyses are kept the same as those in the main analysis. The results were compared with the main ones for validation, with a particular focus on whether there were significant differences between NC and EMCI and whether the general results still held from NC to AD.

### Test–Retest Reliability Assessment

We conducted a third analysis by evaluating test–retest reliability of our method and to check if the main findings could be replicated using another follow-up scan from the same subject. Specifically, we identified a follow-up dataset from several of the NC, EMCI, LMCI and AD subjects in Table 1. A total of 14 subjects (7 males and 7 females) from each group have available retest scans and the average test–retest interval for NC, EMCI, LMCI and AD groups are $9.9 \pm 7.6$, $7.4 \pm 3.9$, $8.8 \pm 3.9$ and $4.8 \pm 1.4$ months, respectively. Retest samples are age ($p = 0.329$, one-way ANOVA, two-tailed with degree of freedom 3) and gender matched.

### External Validation with Independent Dataset

In addition to the ADNI dataset, we also used an independent dataset consisting of 67 NC (65.9 ± 7.2 years old, M/F: 31/36, MMSE = 28 ± 2.1) and 71 amnestic MCI subjects (68.3 ± 9.4 years old, M/F: 33/38, MMSE = 24.4 ± 3.4) and from Xuanwu hospital of Capital Medical University as an out-of-sample validation and reproducibility assessment of our method. The diagnosis of amnestic MCI patients was met the criteria proposed by (Petersen, 2004; Petersen et al., 2001b). The details of the data (e.g., inclusion/exclusion criteria, rs-fMRI protocols) were described (Chen et al., 2016). These two groups have comparable age ($p = 0.1$, 2-sample t-test) and gender ($p = 1$, chi-square test). This dataset is not included in any centers of ADNI project. The same analysis was conducted comparing the differences in 2-connected steady states ($S^B_{11}$ and $S^B_{12}$, as the main analysis indicated that MCI tended to have altered 2-connected steady states compared to NCs).

#### Table 2  Results from Kruskal–Wallis tests comparing dynamic connectedness and 2-connectedness among NC, MCI and AD groups (bold numbers denote significant results after family-wise error corrections)

| Feature | NC/MCI/AD | EMCI/AD | LMCI/AD | AD/NC/MCI |
|---------|-----------|---------|---------|------------|
| $P^C_{11}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{21}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{31}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{41}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{12}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{22}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{32}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{42}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{13}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{23}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{33}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $P^C_{44}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^C_{11}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^C_{12}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^C_{21}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^C_{22}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^B_{11}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^B_{12}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^B_{21}$ | 0.000 | 0.000 | 0.000 | 0.000 |
| $S^B_{22}$ | 0.000 | 0.000 | 0.000 | 0.000 |

Note that FWE indicates significant results after FWE correction.
Results

Dynamic Brain Networks in AD are More Likely Connected in Sparse Settings

As shown in Table 2, 10 out of the 26 features had significant group differences as detected by the three-group comparisons based on Kruskal Wallis tests. Post-hoc analysis revealed that the group differences were mainly contributed by AD (i.e., differences were mainly found in AD vs. NC and in AD vs. MCI), except the 2-connected steady states $S^b_1$ and $S^b_2$, in which MCI also showed differences from NC (Table 3, Fig. 3). For transitions among the connected states, we found that, as long as the connected state #1 (i.e., the brain network is connected at a very sparse setting with only 5% edges) was involved, AD tends to have larger transition probabilities ($P_{11}^c$, $P_{21}^c$, $P_{31}^c$, and $P_{13}^c$, Fig. 3a–d) compared to NC and MCI. These results further led to a steadier connected state #1 in AD ($S^c_1$, Fig. 3h).

These results indicate that AD tends to spend a longer time with the connected network even under a very sparse setting compared to the other groups. Of note, such results do not mean AD tends to have stronger brain dFC; instead, they altogether mean that the AD’s brain tends to have altered dFC that re-distributed the strongest edges to form a more evenly pattern that made the dynamic network more likely connected. On the other hand, AD subjects have to make big changes in terms of the network density (e.g., change from 5 to 15%, and vice versa, Fig. 3c, d) to maintain connectedness status.

If the connected state #3 (i.e., the brain network is connected at a not quite sparse setting with 15% edges) was involved and the previous connected states are also not with a quite sparse setting (10% and 15%, rather than 5%), AD tends to have lower $P_{23}^c$ and $P_{33}^c$ (Fig. 3e, f), possibly due to the dominant findings for $P_{13}^c$ and $P_{31}^c$. All the results from the connected state transition analysis are summarized in the schematic plot (Fig. 3g).

|       | $P_{11}^c$ | $P_{21}^c$ | $P_{31}^c$ | $P_{13}^c$ | $P_{23}^c$ | $P_{33}^c$ | $S^c_1$ | $S^c_3$ | $S^b_1$ | $S^b_2$ |
|-------|------------|------------|------------|------------|------------|------------|--------|--------|--------|--------|
| AD/NC | 0.000      | 0.000      | 0.000      | 0.000      | 0.001      | 0.000      | 0.000  | 0.000  | 0.815  | 0.815  |
| AD/MCI | 0.000      | 0.000      | 0.000      | 0.000      | 0.002      | 0.000      | 0.000  | 0.000  | 0.000  | 0.000  |
| MCI/NC | 0.661      | 0.997      | 0.31       | 0.155      | 0.619      | 0.972      | 0.916  | 0.251  | 0.000  | 0.000  |

*Fig. 3* Group comparisons of each dynamic connected and 2-connectedness metrics among NC, MCI, and AD groups, where **, ***, **** indicate corrected p-values at the intervals of (0.01,0.05], (0.001,0.01], (0.0001,0.001], and (0.00001,0.0001], respectively; error bars show standard errors (SE). Subplot (g) summarize major differences between AD and NC/MCI in terms of the transition probabilities of the connectedness states #1–3 (a–f) as well as the steady connected states (h–i).
Different from the fact that AD’s brain network tends to be connected at a low redundancy situation ($h=5\%$), NC and MCI tend to have connected brain networks in higher redundancy scenarios ($h=15\%$, Fig. 3i). This indicates that NC and MCI (especially NC) tend to spend more time with the connected network under more redundant network settings compared to AD (possibly due to the strong FCs are more distributed within such functional sub-network, which makes the entire network less likely to be connected in a sparse setting).

**2-Connected States Could be Used to Differentiate MCI from NC**

When we checked if the network was, at the same time, 2-connected when it first became connected at the critical point, MCI’s brain network showed a more likely tendency to be also 2-connected compared to NC and AD, with the latter two groups showing similar results (Fig. 3k). In other words, at the critical point, MCI’s brain network was less probable to be only connected but not 2-connected compared to NC and AD (Fig. 3j). Of note, both Fig. 3j, k describe the same difference. However, none of the 2-connected state transition $P_{ij}^R$ showed any group difference. As the steady 2-connected state showed a significant group difference between NC and MCI, this feature might be adopted to detect AD at its preclinical stage.

**Validation Analysis**

We successfully validated the main results by replicating the analysis on newly included subdivided MCI groups (EMCI and LMCI). With MCI replaced with two subgroups, the trends among NC, (E/L)MCI, and AD were largely similar (see Online Appendices) compared to the main results in Tables 2 and 3, except $P_{22}^C$ and $S_4^C$ also showed differences among the four groups. The results of EMCI and LMCI were very similar to each other and all together similar (see Online Appendices) to the results of the single MCI group (Fig. 3). Collectively, separating the MCI into EMCI and LMCI did not change the main conclusions.

More interestingly, we spotted a trend (although it was not significant) with continuous changes from EMCI to LMCI and then to AD (see Online Appendices), especially those for $P_{13}^C$ and $S_4^C$ (see Online Appendices). They indicate that there could be gradual changes in terms of the connected state transitions and LMCI subjects are closer to AD than EMCI. More importantly, as shown in Online Resource the differences in the steady states of 2-connectedness ($S_1^P$ and $S_2^P$) between MCI and NC were preserved in the result of EMCI vs. NC, indicating that the detection of potential AD might be achieved at an even earlier (EMCI) stage.

**Test–Retest Reliability**

After repeating the same analysis on the follow-up data from a subset of each of the four groups used in the validation analysis, we found largely similar results (see Online Appendices). As shown in Online Resource, most of the connectedness and 2-connectedness features from retest data are similar to the results from the test data. We further plotted the strength of the group differences (as defined by transforming the Kruskal Wallis test-derived $p$-values using $-\log(p)$, with a smaller the $p$ indicating a larger group difference) from the test data against those from the retest data. The result indicated an excellent test–retest reliability (with a Spearman correlation $r$ of 0.922) of our method in detection AD-related dynamic network redundancy differences (Fig. 4).

![Fig. 4](image-url) (a) Scatter plot of the four-group comparison results of the $23$ (after removing three same dynamic 2-connectedness features, see definitions of 2-connectedness features) dynamic connectedness and 2-connectedness features based on the test and retest data where $-\log(p)$ quantifies the strength of the group differences. Black and red colors show connected and 2-connected features and round, and diamond shapes indicate transition and steady state features, respectively. The green dashed line represents the threshold $p=0.05/23$ applied to the test data. (b, c) Comparisons of dynamic 2-connected features, $S_1^P$ and $S_2^P$, between NC and amnestic MCI subjects from an independent imaging center (Xuanwu Hospital) for external validation, where * indicates $p<0.05$

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External Validation with Independent Dataset

From the main results, we found that NC and MCI showed significant differences in steady 2-connected states $S^0_2$ and $S^1_2$. Then we checked these two features on the independent data consisting of NCs and amnestic MCIs from Xuanwu Hospital as an external validation. Since $S^0_2$ is essentially reflecting the same difference as $S^1_2$, only one feature was considered. Therefore, no multiple comparison correction was needed. We found that $S^0_2$ (and $S^1_2$) showed a significant difference ($p = 0.015$, Fig. 4b, c) between NCs and amnestic MCIs, similar to the previous findings between NCs and MCIs based on ADNI datasets (Fig. 3j, k).

Discussion

In this paper, we adopted novel brain network attributes, connectedness and 2-connectedness, to quantify dynamic changes in brain chronnectome among different groups at different stages of AD progression. More specifically, we deliberately investigated network connectivity and extended the definition “connectivity” to “2-connectedness”, which is more stringent than “connectivity”. We did not use “connectivity” as a prerequisite for any type of efficiency analysis. Specifically, we used proportional thresholding in our analysis to generate binary networks to measure connectedness and calculate redundancy in the brain network. We paid attention to the connectivity of the brain network and instead of changing the method of getting the network binarized, we focused on the minimum proportional threshold to have the connected network. As mentioned in “5”, in the connected state vector, we represented the minimum density level that the network is connected. Then we revisited those states (the minimum density levels in each sliding window that the network is connected) to check if it is 2-connected or not. Then, we found that these measurements were able to sensitively detect AD-related topological changes in the spatiotemporal brain functional network patterns. Our major findings are as follows. First, we found that AD subjects had a more frequently connected brain network in the sparse setting (Fig. 3a–c, h). It indicates that AD patients tend to maintain a connected brain network for longer time compared to NC and MCI when only the network backbone is considered. Second, we found that AD subjects manifested large temporal fluctuations in terms of the critical points (e.g., with the minimal network density changing from 5 to 15% to maintain connectedness in consecutive temporal windows, Fig. 3c, d) more frequently than NC and MCI. Third, by considering 2-connectedness, subjects with MCI tend to be also 2-connected more frequently at the critical point of connectedness (Fig. 3j, k). The findings imply that, while the MCI’s brain network (together with the NC’s) tends to become connected with denser edges compared to AD’s, it becomes to complete such that the entire network is more likely to be redundant than AD’s network.

The results jointly indicated gradually altered brain network topology in two folds. On one hand, although AD is generally regarded as a disconnection syndrome (with globally decreased FC compared to NC and MCI), they tend to be more connected in a low-density level. This result does not contradict previous findings. This is because the averaged FC weights in AD could be lower than those in NC and MCI, but the strongest FC links in AD could be distributed more evenly from intra to inter-sub-network connections, making the entire network more likely to be connected. Such a status may not be optimal and stable, as the AD’s brain network can sometimes be quite disconnected and needs more weak connections to be included (a higher density) to maintain connectedness (Fig. 3a−d). On the other hand, when considering 2-connected state with redundant connections, subjects who could be in an early stage of AD (MCI) show more differences compared with NC, where the MCI’s brain network features a more robust and redundant topology (larger probability of steady 2-connected state, Fig. 3k) compared with NC and AD. Such an increment of redundancy may help to ensure a back-up path for every shortest path and maintain the network’s efficiency even under random AD pathological damages. As such a phenomenon was only detectable in MCIs, it could be interpreted as an overshot with protective and compensatory effects for MCIs to maintain their cognitive level in the presence of AD-related neurodegeneration (Petersen et al., 2014). More importantly, the MCI’s abnormally elevated redundancy can be detected at an even earlier (i.e., early MCI) stage, indicating good sensitivity of the proposed 2-connectedness measurements. Meanwhile, other authors (Sadiq et al., 2021) also suggested that redundancy may act as a reserve mechanism to safeguard the brain integrity and then support FC to alleviate the cognitive abilities. However, the previous studies mainly focused on measuring the number of connections between nodes without paying attention to the nodes in common among those connections (Kambeitz et al., 2016). In contrast, in this study, we only considered the connections that do not share any nodes in redundant analysis, this can increase the sensitivity of this metric to measure the robustness and resilience of the network in the case of pathological disruption. Utilizing this new redundant metric, we delineated the redundant profile in three functional networks, NC, MCI and AD throughout AD progression and successfully found significant differences among them. To the best of our knowledge, there is no redundancy study comparing patients against healthy controls, though it has some applications in other areas (Quattrociocchi et al., 2014a, b). More specifically, our study focused on redundant analysis of MCI and AD to track the changes in AD.
progression based on rs-fMRI. Our results confirm that from NC to MCI, FC starts redistributing in the brain networks to be able to have more redundant connections to maintain the connectedness of the brain network in response to network disruption due to AD pathology. Then, after disease’s progress, some of these redundant connections may be eliminated by further network impairments, leading to reduced redundancy in AD. Our findings are consistent with previous studies showing that increased functional connectivity within some brain areas may allow the affected individuals to maintain normal behavior despite neuronal loss (Barulli & Stern, 2013; Cabeza et al., 2018). Interestingly, a recent study (Sadiq et al., 2021) reveals that functional redundancy accrues throughout the lifespan to mitigate the effects of age on cognition. Our study further expands this notion to disease condition where functional redundancy dramatically increases in the presence of disease disturbance, which mitigates the effects of pathology on cognition. A critical finding of this study is that although AD represents a more severe disease condition than MCI, MCIs are more discriminative to maintain their cognitive level in the presence of disease condition than MCI, MCIs are more discriminative to maintain their cognitive level in the presence of AD-related neurodegeneration (Cabeza et al., 2018).

It is noticeable that the major findings from the multiple ADNI centers are test–retest reliable and reproducible, with an acceptable external validity based on an independent dataset. For example, we found a significant difference between MCI and NC in steady 2-connected state \( S^0 \) based on the main test (the probabilities for NCs and MCIs are \( 0.56 \pm 0.10 \) and \( 0.44 \pm 0.11 \)), while that from the validation analysis and the retest dataset are very similar \( (0.56 \pm 0.10 \) vs. \( 0.44 \pm 0.08 \) for NCs and EMCIs, and \( 0.58 \pm 0.06 \) vs. \( 0.38 \pm 0.11 \) for the retest data from the same NCs and EMCIs). An independent dataset from Xuanwu Hospital revealed the same trend despite an elevated baseline, where the steady 2-connected state \( S^0 \) from NCs \( (0.62 \pm 0.08) \) were still higher than that from amnestic MCIs \( (0.59 \pm 0.07) \). The effect size on this difference according to Cohen’s d are large \( (1.14 \) for main test, \( 1.32 \) for validation analysis, and \( 2.25 \) for retest, despite a medium one for the independent test \( (0.40) \). The decreased effect size may come from different ethnicities of the subjects from ADNI (mostly Caucasians) and Xuanwu data (all Chinese), different imaging protocols and scanners (e.g., rs-fMRI temporal resolution), different ages and gender ratio (the selected subjects from Xuanwu Hospital are younger than selected ones from ADNI), and/or different MCI diagnostic criteria. Further tests on even larger dataset is necessary to validate our findings.

Graph theory has become a powerful tool in the investigation of brain topological changes in diseased populations including AD (Karwowski et al., 2019). While some previous studies use connectedness as a prerequisite condition to quantify other network attributes (e.g., shortest path length) (Meier et al., 2015), they did not directly compare the connectedness. None of them has ever focused on more redundant network topology such as 2-connectedness. While a handful of previous works have investigated alternative paths (Yoo et al., 2015), none of them examined more stringent connected and 2-connected properties where all pairs of regions must have one (or more than one) independent paths. Our results suggested that these stringent global properties could be quite sensitive in tracking AD progression. We showed the first-ever evidence that time-varying brain connectedness can be informative to understand AD progression. While the majority of the complex brain network studies focused on the shortest paths between regions (Meier et al., 2015) and the derived metrics (e.g., betweenness centrality (Rubinov & Sporns, 2010) and connector hub (van den Heuvel & Sporns, 2013), we showed that other lengthier pathways could be also informative, thanks to the similar concepts and applications in the other fields (Corson, 2010; Härkégård & Glad, 2005; Quattrociocchi et al., 2014a, b; Steiglitz et al., 1969; White & Newman, 2001). To further increase sensitivity, we extend such a concept to dynamic FC network by investigating how the brain changes its reserved paths in a time-varying manner, making it feasible to detect subtle changes in a diseased condition. The framework can be easily applied to other brain diseases and mental disorders.

While the current framework focused on dynamic networks, it is straightforward to apply it to static brain network or a structural connectivity network based on diffusion MRI. In addition, 2-connectedness can be further extended to 3-connectedness (at least three independent paths exist for every pair of brain regions) for network studies in a more redundant scenario. The current work characterized the entire brain network; to improve spatial specificity, one can investigate functional sub-networks (e.g., default mode network) or a sub-network associated with each region for a fine-grained investigation and biomarker detection.

In conclusion, we used novel network redundancy measurements to reveal how dynamic brain functional network changes its topology in more denser conditions during the AD progression. The reliable and reproducible findings provide a new view angle to the AD-related brain networks and a sensitive means to detect AD in its early stage. We advocate that the redundant design is as important as cost efficiency and could be promising for the future network neuroscience studies.
Information Sharing Statement

The source code of the presented method is freely available for use from https://github.com/mghanba/MaryamGhanbariRepository/tree/master.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12021-021-09554-3.

Authors’ Contributions H.Z. and D.S. designed and conceptualized the study and revised the manuscript. M.G. drafted and edited the manuscript, analyzed data, interpreted results. H.Z. played a major role in the interpretation of the results and revision of the manuscript. L.-M.H. analyzed the data and revised the manuscript. Z.Z. and P.-T.Y. analyzed data and revised the manuscript. Y.H. and Y.S. collected and analyzed part of the data and revised the manuscript. All authors read and approved the final manuscript.

Funding M.G. was supported by the National Institutes of Health grants (EB022880 and AG041721). Z.Z., L.-M.H., P.-T.Y. and D.S. were supported by the National Institutes of Health grant (EB022880). Y.H. and Y.S. were supported by National Natural Science Foundation of China (Grants 61633018, 31371007). H.Z. was supported by the National Institutes of Health grants (EB022880 and AG041721). Z.Z., L.-M.H. and P.-T.Y. analyzed data and revised the manuscript. Y.H. and Y.S. collected and analyzed part of the data and revised the manuscript. All authors read and approved the final manuscript.

Availability of Data and Material The time series data from all the subjects as well as the calculated redundancy measurements that support our claims are publicly available at https://github.com/mghanba/MaryamGhanbariRepository/tree/master, upon the manuscript is entering review process.

Code Availability The software we used to calculate connectedness and 2-connectedness is SAGE 8.6 (https://www.sagemath.org). The core function for calculating dynamic redundancy statuses and their transitions are publicly available at https://github.com/mghanba/MaryamGhanbariRepository/tree/master, upon the manuscript is entering review process.

Declarations

Ethics Approval The experiments and data collection were approved by the local ethics committees, as mentioned in ADNI data sharing website http://fad.ni.ion.usc.edu. For the Xuanwu hospital’s data, ethical approval has been obtained from the medical research ethics committee and institutional review board of XuanWu Hospital, Capital Medical University (approval number: [2014]011).

Consent to Participate Data used from ADNI is publicly available, so this is not applicable. For the Xuanwu hospital’s data, all participation is based on written informed consent and the participants will be able to withdraw from the study at any time.

Consent for Publication The publisher has the permission from the authors to publish the paper.

Conflicts of Interest/Competing Interests The authors declare that they have no conflict of interest.

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