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Brain topological alterations related to cognitive changes in Mild Cognitive Impairment and Alzheimer's Disease

Alterazioni topologiche cerebrali in relazione a cambiamenti cognitivi nel Mild Cognitive Impairment e nella malattia di Alzheimer

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Contents

Abstract

Alzheimer's disease (AD) represents the most common neurodegenerative disease. The first clinical symptom that usually brings an individual under clinical attention is the emergence of episodic memory pitfalls, which however occur when the underlying pathology has already reached a certain degree of spreading. In recent years, these neural alterations have been observed to largely overlap with known functional networks, especially the Default Mode (DMN) and the Frontoparietal (FPN) networks. However, much debate exists regarding whether functional alterations can be detected years before symptoms offset, i.e. that is in the prodromal disease stage of Mild Cognitive Impairment (MCI), and their predictive power of MCI-to-AD progression. In this study, we tried to fill this gap by investigating the relationship between topological networks' alteration and the emergence of episodic memory difficulties at 2 years' follow-up. We did so using a recently developed neuroimaging analytic tool, namely graph theory, and a specific battery of tests, assessing all stages of memory encoding, retrieval and recall in a sample of MCI patients and healthy controls. Our results suggest that increased DMN segregation might represent an early biomarker of cognitive worsening in episodic memory encoding. In particular, the study emphasizes that functional compensatory mechanisms in prefrontal nodes of the DMN might be a more prominent feature of the pathology at its prodromal stages, representing an early stressor. These findings might be potentially useful in the early detection of patients at higher risk of clinical progression and for whom resilience boosting interventions might still be put in place.

Introduction

Alzheimer's Disease

Alzheimer's Disease (AD) is considered to be the most common neurodegenerative disease, contributing to 60-70% of dementia cases and therefore representing a recent global public health priority (Leng & Edison, 2021). The main features of AD are extracellular accumulation of proteins, the so-called amyloid plaques, and neurofibrillary tangles, paired helical filaments consisting of hyperphosphorylated tau protein which can be found in the cell's cytoskeleton. Normally, amyloid deposition starts progressing in the isocortex and only later it affects subcortical structures. On the other hand, neurofibrillary tangles typically first affect poorly myelinated limbic neurons in the medial temporal lobe (MTL) (entorhinal cortex and hippocampus), whereas highly myelinated neurons in other temporal, parietal and association cortices are only affected in later stages of the pathology (Jahn, 2013). Along with neurofibrillary tangles (Lane et al., 2018), profound cell loss is also observed in the hippocampal formation (Buckner et al., 2005).

Since the MTL is one of the first regions to present neuropathological changes, the first and most common clinical symptoms are represented by memory difficulties, especially centered on episodic memory (Dickerson & Eichenbaum, 2010). At this phase, it may be possible to make a diagnosis for Mild Cognitive Impairment (MCI) (Lane et al., 2018). This condition is, in fact, usually characterized by an isolated cognitive difficulty, generally centered on episodic memory, with minor or no difficulties in functional abilities (Chandra et al., 2019) and it is often seen as the prodromal phase of AD dementia (Petersen, 2016). In fact, studies have shown that 80% of these patients progress to AD within 6 years follow-up (Lopez, 2013; Petersen, 2016). However, it is important to note

that not all types of MCI are early AD dementia, and that other etiologies can lead to this type of condition (Petersen, 2016). As the disease progresses, the memory loss accelerates, and other cognitive impairments emerge (Lane et al., 2018). In particular, according to the NINCDS-ADRDA criteria, AD symptoms include, among others, deficits in two or more areas of cognition and progressive worsening of memory and other cognitive functions, especially language, motor skills and perception, in absence of other systemic disorders or brain diseases that could account for the symptoms (McKhann et al., 1984). Ultimately, these deficits begin to interfere with the person's autonomy in activities of daily living: at this point, a diagnosis of probable AD dementia can be made. The clinical assessment, and in particular the interview with the patient and an informant and a cognitive examination, represents the mainstay of the diagnosis of probable AD dementia (Lane et al., 2018).

Memory dysfunctions in AD

Generally speaking, memory functions can be divided into two broad categories: implicit, which concerns knowledge of automatized behaviors part of the individual repertoire, e.g., riding a bike, and explicit memory, which instead is concerned with the conscious knowledge and recollection of facts (Budson & Price, 2005). Different categories of explicit memory, related to different neural correlates, exist, and MCI and AD patients usually exhibit impairments across all of them, in particular: semantic, episodic and working memory (Budson & Price, 2005). Moreover, impairments in explicit memory are usually seen as the defining symptom of MCI (Chandra et al., 2019). For instance, a large number of studies have suggested that the semantic storage in AD may present disruptions which could possibly arise years prior to diagnosis and affect the patient's

language, especially verbal fluency and naming (Jahn, 2013). Semantic memory can be defined as a memory system storing factual and conceptual knowledge without referring to any particular context (Budson & Price, 2005). The disruption of this memory system in AD seems to be attributable to neuropathology in the inferolateral temporal lobes and in frontal cortices, leading to poor activation and therefore retrieval of semantic information (Jahn, 2013).

Working memory, defined as the ability to temporarily maintain and manipulate information needed to complete a task, uses a vast network of cortical and subcortical areas among which the prefrontal cortex (PFC), which oversees the selection of relevant information from the environment and ultimately enables its manipulation (Budson & Price, 2005; Curtis & D'Esposito, 2003). In AD, the disruption of this memory storage is thought to be related to damages to frontal subcortical circuits that normally occur as the disease reaches advanced stages of neuropathology (Jahn, 2013).

Episodic memory is defined as a memory system used to store and recall personal experiences, framed in the context (Budson & Price, 2005). In typical AD, the progression of clinical symptoms follows a sequential order, starting with episodic memory impairments, which occur long before the diagnosis of AD dementia, followed by semantic memory difficulties and ultimately by working memory disruption, meaning that episodic memory is the first memory storage to be involved from the earliest stages of MCI (Talwar et al., 2021). Difficulties in encoding and retrieval of episodic memories in MCI and AD patients are probably correlated to the disruption of an intricate network which includes different brain regions, notably the PFC, the MTL and the parietal posterior cortex (PPC)(Jahn, 2013). An in-depth explanation on the neural substrates of

episodic memory and their relationship to the AD pathology is provided in the following paragraph.

Networks dysfunctions associated with episodic memory impairments in AD

From a neurological point of view, global dysfunction, more than local alterations, have recently been recognized as a core feature of the AD brain. These alterations occur as cascades of structural and functional failures that follow specific spreading patterns, partially overlapping with known functional resting state networks (Buckner et al., 2005). In recent years, innovations in brain imaging have allowed detection of characteristic disruptions in functional networks in AD, particularly through resting-state functional magnetic resonance imaging (fMRI). FMRI is a neuroimaging technique used to depict brain activity by measuring changes in blood flow, the oxygen level-dependent (BOLD) signal, allowing the study of spontaneous region-to-region communication in the brain. Notably, communication across the brain self-organizes in functional brain networks, which are known to serve different sensitive (Visual, Auditory and Somatomotor networks) and cognitive (Frontopariatal, Limbic, Default Mode, Dorsal and Ventral Attention networks) functions (Chandra et al., 2019). The Default Mode Network (DMN) and the Frontoparietal Network (FPN) are especially known to be altered in the AD pathology (Badhwar et al., 2017).

The DMN is recognized as the core network of the human brain during resting-state. It can be roughly divided into four distinguished subdivisions: the ventral medial prefrontal cortex (VMPFC); the dorsal medial prefrontal cortex (DMPFC); the posterior cingulate cortex and precuneus plus the lateral parietal cortex and the entorhinal cortex. The

VMPFC plays an important role in receiving external information and redirects that information to structures such as the hypothalamus, the amygdala, the periaqueductal gray matter. Therefore, the VMPFC is a key area for social behavior, mood control, motivational drive and personality (Raichle, 2015). The DMPFC, on the other hand, is involved in self-referential judgments (Raichle, 2015). Finally, the posterior cingulate cortex and the medial precuneus, along with the lateral and parietal components of the DMN, are associated with recollection and retrieval of previously encoded information (Raichle, 2015). Overall, the DMN appears hence to be involved in episodic memory processing, mental imagery and internal dialogue, and the strength of its characteristic negative correlation (i.e., antiphase) with the oscillatory activity of other networks has been promoted as a marker of good cognitive functioning and healthy aging (Vatansever et al., 2018). In AD, the loss of functional connectivity (FC) between DMN components mirrors disease progression and the associated cognitive symptoms from the earliest stages of MCI (Jones et al., 2016). In particular, a decrease FC in posterior and an increase FC in anterior and ventral DMN regions has been seen since the early stages of MCI and to eventually result in complete functional disconnection within 2-4 years from the AD diagnosis (Chandra et al., 2019).

As opposed to the DMN, the FPN is crucial when cognitive effort is required, therefore showing opposite activation patterns with the DMN during cognitive processes (Badhwar et al., 2017). The FPN, which includes portions of the lateral prefrontal cortex (lPFC) and PPC, is believed to be a control network especially involved in a wide variety of tasks by modulating cognitive control abilities (Zanto & Gazzaley, 2013). In particular, it selects and represents relevant stimuli (Reineberg et al., 2015), directs attention (Zanto & Gazzaley, 2013) and provides flexibility by adjusting responses according to feedback

(Marek & Dosenbach, 2018). Similarly to the DMN, connectivity within the FPN is also disrupted in MCI and AD patients, characterized by a significant reduction in FC within PPC regions (Yang et al., 2023). Moreover, decreased positive correlations between prefrontal and parietal regions have been observed, suggesting that an anterior-posterior disconnection may be a key feature of the AD brain (Wang et al., 2007). On the other hand, some findings suggest that AD patients show increased activity and connectivity, especially within prefrontal areas and other brain regions such as parietal, occipital and temporal lobes (Sanz-Arigita et al., 2010). This evidence suggests that decreased connectivity is found mainly between lobes, whereas increased connectivity is mainly within lobes, implying that the increase within-lobe connectivity represents a compensatory effect for the reduced connectivity between lobes (Wang et al., 2007).

Of particular relevance for the study of AD, both the DMN and the FPN show a specific involvement in distinct stages of episodic memory encoding and retrieval. Episodic memory retrieval strongly depends on the efficient storage of events' features when they are encoded (Shimamura, 2011, 2014). The reconstruction of source memory, seen as the memory for the contextual features such as time, place, people, thoughts and feelings, is an essential, if not defining feature of episodic memory, and it strongly contributes to the success of episodic retrieval (Shimamura, 2011, 2014). Neuroimaging studies have shown that the PFC and the MTL are robust neural correlates of both episodic encoding and retrieval; for instance, after the activation of bottom-up sensory processes in response to sensory stimuli, the PFC, part of the FPN, holds online the features defining the event as a working memory representation, selecting, maintaining and updating this information, whereas during retrieval, it searches through memory and activates pertinent event feature (Sestieri et al., 2011; Shimamura, 2011, 2014). More specifically, the

ventrolateral PFC participates in the maintenance of event features and initiates retrieval, while the dorsolateral PFC plays an important role in the updating and the manipulation of retrieved features (Shimamura, 2011, 2014).

The role of the MTL, consisting of the hippocampus and surrounding entorhinal, perirhinal and parahippocampal cortices, has been pointed out since the landmark neurological case of Henry Molaison, a patient who underwent an invasive operation consisting in the removal of the anterior MTL and that, as a result, lost his ability to remember episodic events (Neylan et al., 2000; Corkin, 2013; Shimamura, 2014). The MTL is a key structure for episodic memory, since it links coactive event features such as feelings, sights, time, place, people stored in different neocortical regions and plays a decisive role in binding source memory, seen as a single totality of those event features, facilitating therefore the reactivation or the replay of episodic memories and enabling their recollection at a later time (Shimamura, 2011). In recent years, numerous studies have reported the PPC as particularly involved in episodic memory and as one of the most, if not the most, activated region during the episodic retrieval (Naghavi & Nyberg, 2005; Sestieri et al., 2011; Shimamura, 2011, 2014). More specifically, three PPC regions appear to be particularly implicated in this process: the dorsal PPC (superior parietal lobule, intraparietal sulcus), the ventral PPC (supramarginal gyrus, angular gyrus, temporal-parietal junction, and temporal-parietal junction), and the medial PPC (precuneus, retrosplenial cortex, posterior cingulate cortex) (Sestieri et al., 2011; Shimamura, 2011, 2014). Among these regions, the ventral PPC (vPPC) appears to be the most involved in episodic retrieval and source recollection, as its activation has shown in different studies strong positive correlations with the success of healthy controls in correctly identifying items as “old”(Sestieri et al., 2011; Shimamura, 2011). To better

understand the involvement of vPPC in episodic memory, a large number of theories have been proposed in literature. According to one of the most recent, the Cortical Binding of Relation Activity (CoBRA), the vPPC constitutes a convergence zone, binding episodic features together within the neocortex (Sestieri et al., 2011; Shimamura, 2011, 2014). To better understand its role in this process, it has to be noted that this region is often seen and described as a crossroad between the parietal, the temporal and the occipital cortices and it has intricate connections with the dorsal visual path, the ventral visual path, the MTL and the PFC, hence constituting a geographical central and well-connected region able to establish intermodal associations with diverse event features (spatial, acoustic, verbal) (Shimamura, 2011). The cortical binding operated by the vPPC works in parallel with the MTL, since the reactivation of episodic memories driven by the MTL induces the formation of neocortical bindings within the vPPC (Shimamura, 2011). In other words, according to this model, the vPPC would reinforce the inter-feature connections at a later stage, binding episodic memories within the neocortex (Shimamura, 2011). In AD, since the MTL and the PFC, part of the DMN, and the PPC, part of both the DMN and the FPN, are regions specifically targeted by the pathology and functionally disrupted, this system becomes deficient, although much debate exists on whether these issues are more related to difficulties in encoding, retrieval or both (Tromp et al., 2015).

Graph theory in AD

Graph theory is a recently developed analytical tool used to study complex interactions between components of a system, with applications ranging from the study of communication systems, social networks, power grids distribution, as well as biological ensembles (Albert & Barabasi, 2002). When applied to the brain, graph theory has been

widely employed to better investigate the information exchange between regions, represented as nodes, and their functional connections, represented as edges (Dennis & Thompson, 2014; Rubinov & Sporns, 2010). Investigating the brain as a graph holds several advantages, among which generalizability and interpretability (Bullmore & Bassett, 2011). For example, we can look at the topological properties of networks' nodes to estimate global and local efficiency in information transfer between network's components. Few examples of those measures include indexes of integration, such as the degree of connectivity of one node to the other nodes in the network (Nodal Degree) or the average distance between nodes in the network (Characteristic Path Length); as well measures of segregation, such as the tendency of nodes to clusterize and form triangular triples (Clustering Coefficient) or the extent for which a network can be divided in independent modules (Modularity) (Farahani et al., 2019). Taking advantage of such methodology, several studies in the literature have investigated network's alterations in the MCI-AD continuum, reporting less interconnectivity and more segregated clusters in the DMN of AD patients compared to healthy controls (Çiftçi, 2011; delEtoile & Adeli, 2017). Moreover, neuroimaging studies investigating FC have shown a similar pattern in MCI patients, reporting functional disruption in the DMN with a tendence for clusterization, but with a less marked inter-connectivity decrease compared to the AD brain (delEtoile & Adeli, 2017).

While there is good evidence of functional disruption within the DMN and the FPN in MCI and AD, a more precise understanding of how these patterns of altered connectivity may contribute to the early clinical symptoms, notably memory impairments, is still missing.

The current study

To this aim, we investigated if altered communication within DMN and FPN nodes is present in MCI patients and if it can be predictive of episodic memory impairments over a time window of 2 years. Furthermore, we aimed to do so using graph theory analysis and a specific battery of tests assessing all stages of memory encoding, retrieval and recall to shed light on the association between topological alterations and memory impairments. The identification of early biomarkers of pathology represents indeed the most current challenge in AD studies (Humpel, 2011; Sharma, 2016), as it might help direct interventional therapies to counteract disease progression. Moreover, functional connectivity may represent a truly advantageous biomarker, since fMRI is a non-invasive imaging technique that does not require injections, as in lumbar punctures or blood withdrawal, or radiation exposure, as in positron emission tomography (PET), and can therefore be repeated many times in longitudinal studies.

1. Methods

1.1 Participants

Longitudinal data of 41 healthy controls (HC, mean age: 71 ± 5.83; mean education:16.6±2.1; 22 males; 35 right-handed) and 32 MCI (mean age: 69.9 ± 9.11; mean education: 15.7±2.3; 17 males; 27 right-handed) patients were retrieved from the Alzheimer Disease Neuroimaging Initiative, third phase of the project (ADNI3, https://adni.loni.usc.edu/). Inclusion criteria for HC participants include: Mini-Mental State Exam (MMSE) score between 24 and 30, a Clinical Dementia Rating (CDR) score of 0 and absence of significant impairment in cognitive functions or activities of daily

living. On the other hand, MCI patients meet the following inclusion criteria: MMSE score between 24 and 30 inclusive, CDR of at least 0.5, general cognition and functional performance sufficiently preserved such that a diagnosis of AD cannot be made. Participants suffering any significant neurologic disease were excluded (Weiner et al., 2016). Demographic characteristics of sample participants are detailed in Table 1.

	HC	MCI	t-test
Education	16.6±2.1	15.7±2.3	$t_{(73)} = 1.75$, $p = 0.08$
Age	71±5.8	69.9±9.1	$t_{(73)} = 0.64$, $p = 0.5$
MMSE	29±1.4	27.9±2.2	$t_{(73)} = 2.93$, $p = 0.004$

Table 1. Demographic characteristics of HC and MCI participants considered in this study.

1.2 Cognitive evaluation

The ADNI project's clinical core includes an extensive test battery; however, for the purpose of our study, we chose to focus on two scales, the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) (Kueper et al., 2018; Weiner et al., 2016), which assesses the participant's general cognitive functioning and it is often employed in pre-dementia studies, and a measure specifically developed to assess memory functions: the Embic Corporation Digital Cognitive Biomarkers (DCBs) scale (Bock et al., 2022).

The ADAS-COG is a structured scale to assess the level of cognitive dysfunction in AD and pre-clinical populations (Kueper et al., 2018; Weiner et al., 2016). It includes a number of tasks evaluating memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs)

(Weiner et al., 2016). On the other hand, the DCBs scale was specifically developed to quantify latent cognitive processes that underlie memory functions. (Bock et al., 2022). The DCBs results from the application of a hierarchical Bayesian cognitive processing to scores from wordlist memory tests commonly used to test learning, recall and recognition. This approach allows to study in a more subtle but distinct way cognitive changes at processes that are not quantifiable using observed behaviors. The model results in seven scores, each representing the probability of the information being processed through different encoding (N1, N2, N3, N4) or retrieval (R1, R2, R3), to and from three distinct storage stages (pre-task, transient, durable) (see Table 2). Three measures (M1, M2, M3) have been added, quantifying the probability of recall from transient storage on immediate recall tasks, durable storage on immediate recall tasks and durable storage on delayed recall tasks (see Table 2).

DCBs	Correlate	Description
N1	Encoding	Probability of encoding into the DURABLY LEARNED State
N2	Encoding	Probability of encoding into the TRANSIENTLY LEARNED State
N3	Encoding	Probability of encoding into the DURABLY LEARNED State, following previous TRANSIENT LEARNING (N2)
N4	Encoding	Probability of encoding into the DURABLY LEARNED State, due to successful retrieval (R1) from the TRANSIENTLY LEARNED State
R1	Retrieval	Probability of retrieving from the TRANSIENTLY LEARNED State
R2	Retrieval	Probability of retrieving from the DURABLY LEARNED State

R3	Retrieval	Probability of retrieving from the DURABLY LEARNED State after a 5-minute delay with distraction
M1	Recall	Probability of immediate recall of a non-durably stored episodic memory
M2	Recall	Probability of immediate recall of a durably stored episodic memory
M3	Recall	Probability of delayed recall of a durably stored episodic memory

Table 2. Available Digital Cognitive Biomarkers. Description of available scores, each representing the probability of the information being processed through different encoding (N1, N2, N3, N4), retrieval (R1, R2, R3), and recall (M1, M2, M3) stages. Adapted from Bock et al., 2022.

Three different wordlists were used across different visits; for each visit, wordlists were presented in a shuffled way to prevent the accumulative serial position effects of primacy and recency on encoding. A normative adjustment was therefore developed and applied to the wordlists (Bock et al., 2022).

For the purpose of this study, we analyzed the scores of the aforementioned neuropsychological batteries that were collected at baseline and after two years for all participants.

1.3 Neuroimaging data

T1-weighted anatomical data [repetition time (TR) = 2300 ms, time interval (TI) = 900 ms, matrix size = 208 x 240 x 256mm, voxel size = 1x1x1mm] and functional resting state data [acquisition parameters: number of volumes = 195, TR = 3000ms, TE = 30ms, matrix size = 220 x 220 x 160mm, voxel size = 3.4 mm^3, flip angle (FA) = 90 deg.] were collected according to the ADNI3 guidelines (https://adni.loni.usc.edu/adni-3/). All

processing of brain data was performed in FSL (Jenkinson et al., 2012). The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 6.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0 s). Slice timing correction was also performed to correct for differences in time acquisition of the fMRI volumes. Then, FLIRT was used to co-register each participant's functional and anatomical volume using the normalized mutual information as a cost function and 6-degree-of-freedom. Finally, the brain was parceled into 200 regions of interests (ROIs) according to the Schaefer Atlas (Schaefer et al., 2018). Functional connectivity matrices were then computed from the individual time series and further transformed into Fisher's z-scores to ensure normality.

1.4 Graph theory measures extraction

The study of brain connectivity was approached based on the mathematical principles of graph theory. In order to extrapolate graph theory measures, a NxN connectivity matrix is constructed for each individual by correlating the fMRI timeseries of activation in all pairs of parcellated regions (Dennis & Thompson, 2014; Rubinov & Sporns, 2010). Then, the full matrix is thresholded to retain only the 10% to the 40% of strongest connections (Bullmore & Bassett, 2011). Such a stringent approach is necessary to reduce the risk of false positive connections in the graph while allowing to clearly distinguish the single units of the network (Sinclair et al., 2015). To measure the efficiency of the information flow in the system, we focus on four graph theory metrics extracted via Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) functions running in MATLAB 2017b, looking at *integration measures*:

i) Characteristic Path Length (CharPath): the average distance between a node and all the other nodes of the system.

ii) Global Efficiency (Eglob): the inverse of the average shortest path, thus quantifying the amount of information shard across the whole network.

and *segregation measures*:

iii) Clustering Coefficient (ClusCoef): the fraction of nodes being neighbors with the surrounding nodes, forming triangular triplets.

iv) Local Efficiency (Eloc): the inverse of the average shortest path connecting a node to all other nodes of the system, thus quantifying the amount of information shared within the neighborhood.

To test our hypothesis, such measures were extracted separately from the DMN and the FPN (network-level analysis), as well as their individual nodes (node-level analysis).

1.5 Statistical Analyses

Statistical analyses were run in Matlab 2017b (The Mathworks, Inc., Natick, MA, USA). At the network level, we first tested for differences in the topography of the DMN and FPN between HC and MCI patients by means of paired t-tests (significance level, $p<0.05$ FDR-corrected). Then, multiple linear regression models were run to test the power of topological measures of DMN and FPN in predicting cognitive decay over a 2 years' temporal window, as reported in the formula below:

$$\text{CognitiveMeasure}_{y2} \sim \text{CharPath}_{baseline} * group + \text{Eglob}_{baseline} * group + \text{ClusCoef}_{baseline} * group + \text{Eloc}_{baseline} * group + \text{CognitiveMeasure}_{baseline} * group \quad (1)$$

In this formula (1):

$CognitiveMeasure_{y2}$ = ADAS composite score and EMBIC scores at year 2

Group = interaction term

$CharPath_{baseline}$ = Characteristic Path Length at baseline

$Eglob_{baseline}$ = Global Efficiency at baseline

$ClusCoef_{baseline}$ = Clustering Coefficient at baseline

$Eloc_{baseline}$ = Local Efficiency at baseline

$CognitiveMeasure_{baseline}$ = ADAS composite score and EMBIC scores at baseline

To test if topological measures can be predictive of clinical decay in MCI patients compared to HCs, an interaction term (group) was added to the model. Importantly, baseline score measures were considered as a covariate to better model cognitive decay as a function of the individual starting point. Outliers were removed based on the models' residuals. The significant threshold was set as $p < 0.05$. To reduce the risk of false positive results, only measures that proved to be significant across the thresholds tested (90-80-70-60%) are reported and further discussed. To control for the risk of multicollinearity, the Variance Inflation Factor (VIF) was computed among all predictors in the formula, proving null to little collinearity between the variables.

Finally, based on the significant results obtained at the network level in predicting memory performance at 2 years follow-up, we further investigated these measures at the single node level. In more details, t-tests were performed to test for differences in nodes' topography between MCI and HC at baseline and after 2 years. To reduce the risk of false positives, only results surviving permutation (n=1000) correction were reported. Afterwards, multiple regression models were run again as reported in formula (1), but this time with the single nodes' graph measures as predictors.

2. Results

In this study, we tested the predictive power of functional alterations in the communication within the DMN and the FPN as possible early biomarkers of subsequent cognitive decay over a temporal window of 2 years. Longitudinal data on the cognitive fitness of our participants were collected based on a i) general index derived from the ADAS-COG scale and a ii) specific memory measure retrieved from the DCBs battery. Results are presented at the network- and node-level.

2.1. Network-level results

DMN

Topography

A significant difference in the topography of the DMN network was observed between HC and MCI patients for the segregation measures of clustering coefficient ($t_{(71)} = 3.21$, $p_{corr} = 0.007$); and local efficiency ($t_{(71)} = -2.39$; $p_{corr} = 0.03$), but not for the integration measures of characteristic path length ($t_{(71)} = 0.13$, $p_{corr} = 0.89$) or global efficiency ($t_{(71)} = -0.81$, $p_{corr} = 0.55$) (see Figure 2).

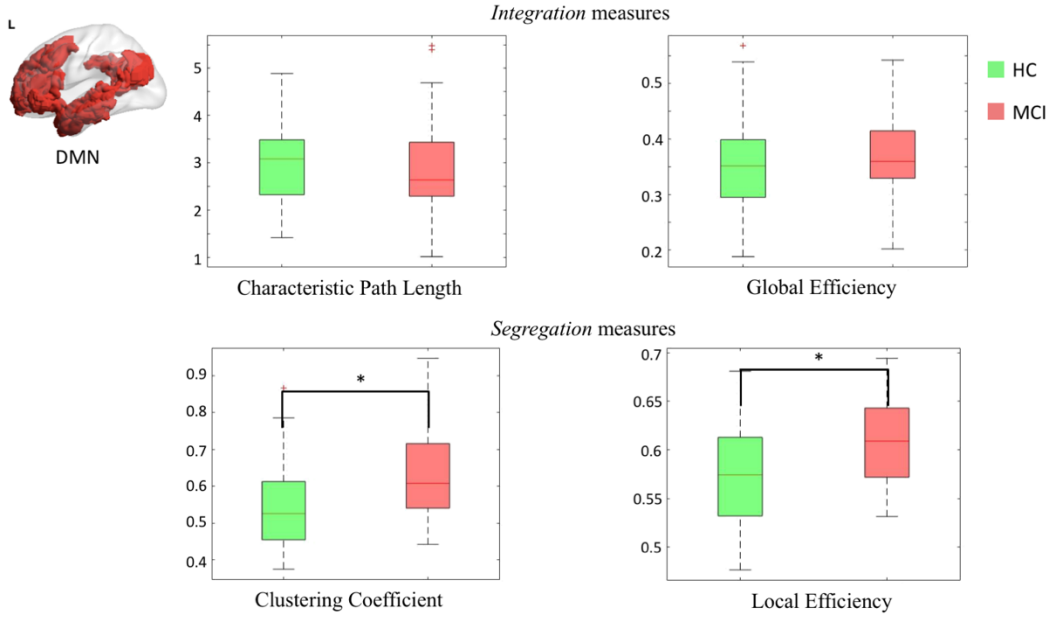

Figure 2. Boxplot of topography measures computed for the DMN. Significant higher measures of clustering coefficient and local efficiency were observed for MCI patients compared to HC.

*p <0.05, FDR-corrected

ADAS-COG

No graph theory measure was found to be predictive of individuals' performance at the ADAS-COG scale, neither for the DMN ($R^2 = 0.714$, $F_{(59)} = 13.4$, $p = <0.0001$), nor for the FPN ($R^2 = 0.613$, $F_{(58)} = 8.33$, $p = <0.0001$). A significant positive correlation was observed between baseline ADAS-COG scores and the ADAS-COG scores collected after 2 years for both the DMN ($\beta = 0.77$, $p = < 0.0001$) and the FPN ($\beta = 0.63$, $p = 0.0002$).

DCBs

Encoding (N1-N2-N3-N4)

After running a multiple regression model ($R^2 = 0.367$, $F_{(41)} = 2.16$, $p = 0.036$), we found a significant positive correlation between the measure of clustering coefficient and DCBs' N1- probability of encoding into the durable learned state ($\beta = 0.77$, $p = 0.016$). Moreover, a significant interaction term between clustering coefficient and group was found ($\beta = -0.84$, $p = 0.028$) (see Figure 3A), as well as a significant interaction between baseline and group ($\beta = 0.64$, $p = 0.022$) (see Figure 3B). These results remained consistent at different thresholds (90-80-70-60%, see Appendix I).

On the other hand, no other graph theory measure was observed to significantly predict other encoding scores: N2 ($R^2 = 0.0748$, $F_{(41)} = 0.301$, $p = 0.982$), N3 ($R^2 = 0.275$, $F_{(41)} = 1.42$, $p = 0.203$), N4 ($R^2 = 0.217$, $F_{(41)} = 1.03$, $p = 0.435$).

Retrieval (R1-R2-R3)

After running a multiple regression model ($R^2 = 0.414$, $F_{(41)} = 2.63$, $p = 0.0122$), we found a significant positive correlation between the measure of local efficiency and scores obtained at DCBs' R3 - probability of retrieving from the durably learned state after a 5-minute delay with distraction ($\beta = 0.64$, $p = <0.01$) (see Figure 3C). These results remained consistent at different thresholds (80-70-60%, see Appendix I). On the other hand, no other graph theory measure was observed to significantly predict other retrieval scores: R1 ($R^2 = 0.157$, $F_{(41)} = 0.692$, $p = 0.739$), R2 ($R^2 = 0.335$, $F_{(41)} = 1.79$, $p = 0.09$).

Recall (M1-M2-M3)

No graph theory measure was found to be predictive of individuals' recall performance: M1 ($R^2 = 0.319$, $F_{(40)} = 1.7$, $p = 0.108$), M2 ($R^2 = 0.488$, $F_{(41)} = 3.55$, $p = 0.00148$), M3

($R^2 = 0.361$, $F_{(41)} = 2.11$, $p = 0.0419$). Baseline scores were observed to be a significant predictor of recall for M2 ($\beta = 0.67$, $p = 0.0003$) and M3 ($\beta = 0.5$, $p = 0.01$) scores.

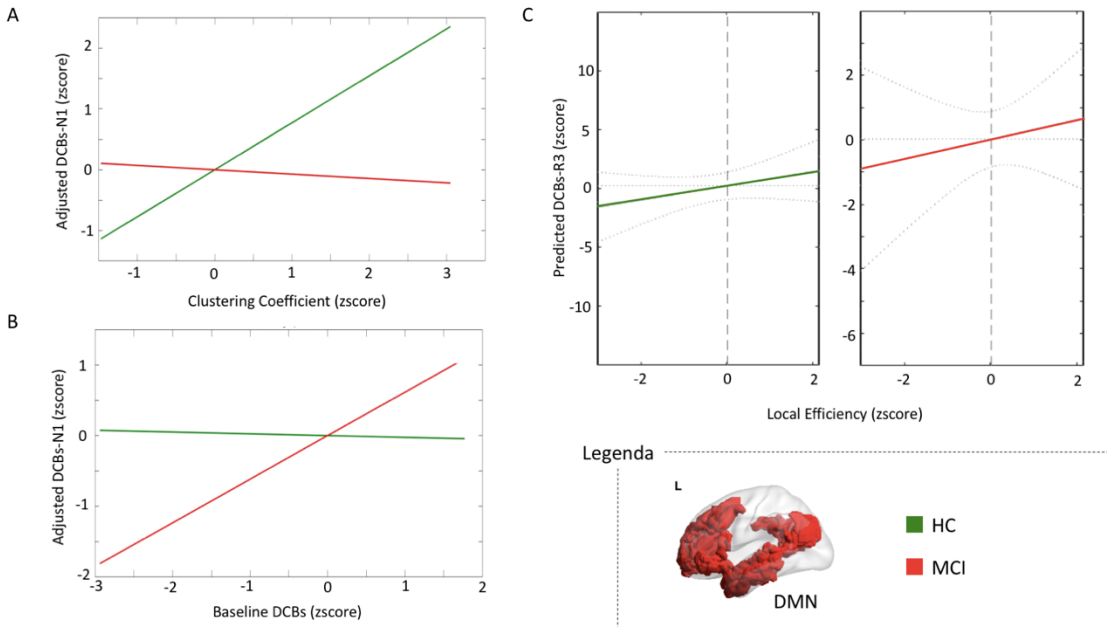

Figure 3. **DMN topological predictors of future memory impairments. A**. A significant positive association can be appreciated between baseline DMN clustering coefficient measures and individual scores at DCBs - N1 measured 2 years after. This association appears to be present in the HC group, but lacking in the MCI group. **B**. DCBs - N1 baseline scores significantly predicted scores collected after 2 years in our MCI group. HC did not show significant changes in score as a function of time. **C**. DMN local efficiency measures were observed to positively predict DCBs-R3 scores at 2 years follow-up with no difference between our HC and MCI groups.

FPN

Topography

No significant differences in the topography of the FPN network were observed between HC and MCI patients for the measures of characteristic path length ($t_{(71)} = 1.48$, $p_{corr} =$

0.28), global efficiency ($t_{(71)}$ = -1.12, p_{corr} = 0.35), clustering coefficient ($t_{(71)}$ = 1.96, p_{corr} = 0.21) and local efficiency ($t_{(71)}$ = 0.35, p = 0.72) (see Figure 4).

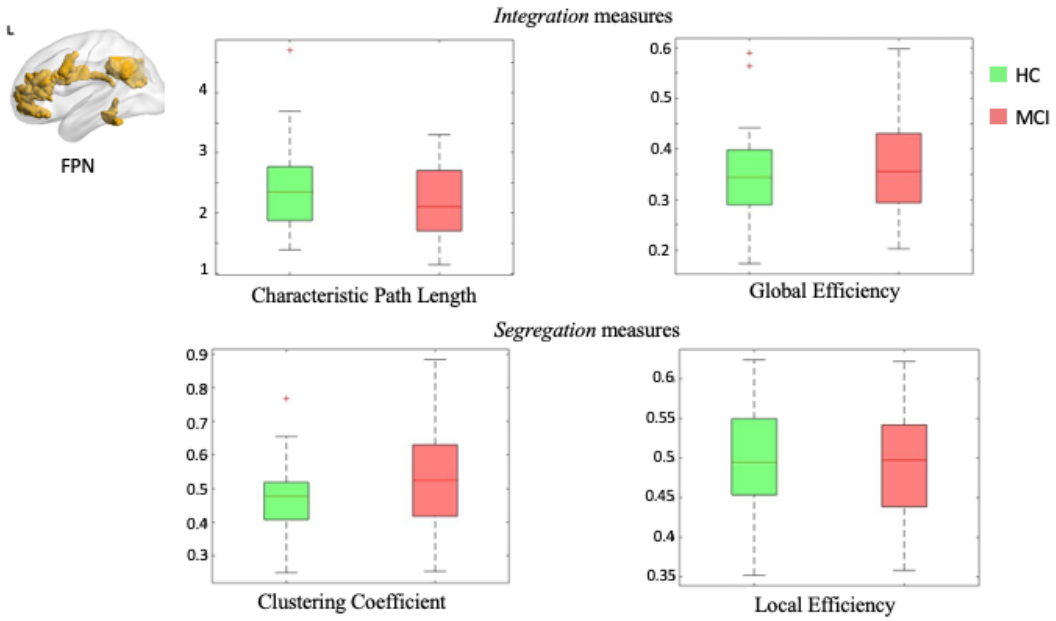

Figure 4. Boxplot of topography measures computed for the FPN. No significant differences were observed in the topography of the FPN between HC and MCI.

DCBs

Encoding (N1-N2-N3-N4)

After running a multiple regression model (R^2 = 0.899, $F_{(40)}$ = 1.6, p = 0.136), we found a significant positive correlation between the measure of clustering coefficient and scores obtained at DCBs' N2 - probability of encoding into the transiently learned state (β = 0.64, p = <0.01). Despite the fact that the model did not emerge as significant, its main effects reached instead the statistical threshold consistently for all thresholds (80-70-60%, see Appendix I). The meaning behind this finding is further interpreted in the discussion.

On the other hand, no other graph theory measure was observed to significantly predict other encoding scores: N1 ($R^2 = 0.296$, $F_{(40)} = 1.57$, $p = 0.146$), N3 ($R^2 = 0.26$, $F_{(41)} = 1.31$, $p = 0.253$), N4 ($R^2 = 0.3$, $F_{(41)} = 1.5$, $p = 0.134$).

Retrieval (R1-R2-R3)

No graph theory measure was found to be predictive of individuals' retrieval performance: R1 ($R^2 = 0.269$, $F_{(41)} = 1.37$, $p = 0.222$), R2 ($R^2 = 0.217$, $F_{(41)} = 1.03$, $p = 0.438$), R3 ($R^2 = 0.407$, $F_{(41)} = 2.55$, $p = 0.0146$). Baseline scores were observed to be a significant predictor of retrieval for R3 ($\beta = 0.46$, $p = 0.01$) scores.

Recall (M1-M2-M3)

No graph theory measure was found to be predictive of individuals' recall performance: M1 ($R^2 = 0.353$, $F_{(41)} = 2.04$, $p = 0.0493$), M2 ($R^2 = 0.492$, $F_{(41)} = 3.61$, $p = 0.00128$), M3 ($R^2 = 0.507$, $F_{(41)} = 3.84$, $p = 0.0008$). Baseline scores were observed to be a significant predictor of retrieval for all DCBs: M1 ($\beta = 0.5$, $p = 0.005$), M2 ($\beta = 0.6$, $p = 0.0003$), M3 ($\beta = 0.5$, $p = 0.0008$).

2.2. Node-level results

At baseline, 7 nodes belonging to the DMN showed significantly higher clustering coefficient in the MCI patients compared to HC. After 2 years, an even higher number of DMN nodes, especially frontal nodes, showed a marked difference between HC and MCI (see Table 3; Figure 5A). The same pattern was observed for the measure of local

efficiency, which was also observed to be higher in the DMN nodes of MCI patients compared to HC at baseline and even more so after 2 years (see Table 4; Figure 5B).

Clustering coefficient					
Baseline			**Y2**		
Left-SupTemp Gyrus	Node [-58 -42 8]	$t_{(71)} = -2.03$; $p_{corr} = 0.01$	Left-DorsalACC	Node [-6 44 8]	$t_{(71)} = -2.22$; $p_{corr} = 0.004$
Left-DorsalACC	Node [-6 44 8]	$t_{(71)} = -2.56$; $p_{corr} = 0.004$	Left-AntPFC	Node [-8 60 20]	$t_{(71)} = -3.39$; $p_{corr} = 0.0001$
Outside defined BAs	Node [-6 30 24]	$t_{(71)} = -2.89$; $p_{corr} = 0.0001$	Left-VentAntCing	Node [-6 30 24]	$t_{(71)} = -3.11$; $p_{corr} = 0.003$
Outside defined BAs	Node [-24 24 48]	$t_{(71)} = -2.85$; $p_{corr} = 0.004$	Left-dlPFC(dorsal)	Node [-12 48 44]	$t_{(71)} = -3.03$; $p_{corr} = 0.0001$
Outside defined BAs	Node [8 58 18]	$t_{(71)} = -2.69$; $p_{corr} = 0.008$	Left-dlPFC(dorsal)	Node [-4 34 44]	$t_{(71)} = -2.29$; $p_{corr} = 0.02$
Outside defined BAs	Node [16 46 44]	$t_{(71)} = -2.77$; $p_{corr} = 0.0001$	Right-FrontEyeField	Node [8 42 4]	$t_{(71)} = -2.19$; $p_{corr} = 0.03$
Right-DorsalPC	Node [12 -54	$t_{(71)} = -2.62$; $p_{corr} = 0.02$	Right-AntPFC	Node [8 58 18]	$t_{(71)} = -4.47$;

C	14]				p_{corr} = 0.0001
			Outside defined BAs	Node [16 46 44]	$t_{(71)}$ = -2.05; p_{corr} = 0.005
			Right-FrontEyeField	Node [28 30 42]	$t_{(71)}$ = -2.41; p_{corr} = 0.006
			Right-VisMotor	Node [6 -58 44]	$t_{(71)}$ = -2.21; p_{corr} = 0.01

Table 3. Nodes' level analyses-clustering coefficient. MNI coordinates (x; y; z).

Local efficiency					
Baseline			**Y2**		
Right-FrontEyeField	Node [-6 30 24]	$t_{(71)}$ = -2.05; p_{corr} = 0.02	Outside defined BAs	Node [-8 60 20]	$t_{(71)}$ = -2.93; p_{corr} = 0.001
Left-FrontEyeField	Node [-24 24 48]	$t_{(71)}$ = -2.31; p_{corr} = 0.01	Left-VentAntCing	Node [-6 30 24]	$t_{(71)}$ = -2.43; p_{corr} = 0.03
Outside defined BAs	Node [16 46 44]	$t_{(71)}$ = -2.02; p_{corr} = 0.03	Left-dlPFC(dorsal)	Node [-12 48 44]	$t_{(71)}$ = -2.59; p_{corr} = 0.0001
			Left-DorsalPCC	Node [-10 -56 12]	$t_{(71)}$ = 2.25; p_{corr} = 0.03
			Right-AntPFC	Node [8 58 18]	$t_{(71)}$ = -4.05; p_{corr} = 0.0001

	Outside defined BAs	Node [28 30 42]	$t_{(71)} = -2.51$; $p_{corr} = 0.008$

Table 4. Nodes' level analyses- local efficiency. MNI coordinates (x; y; z).

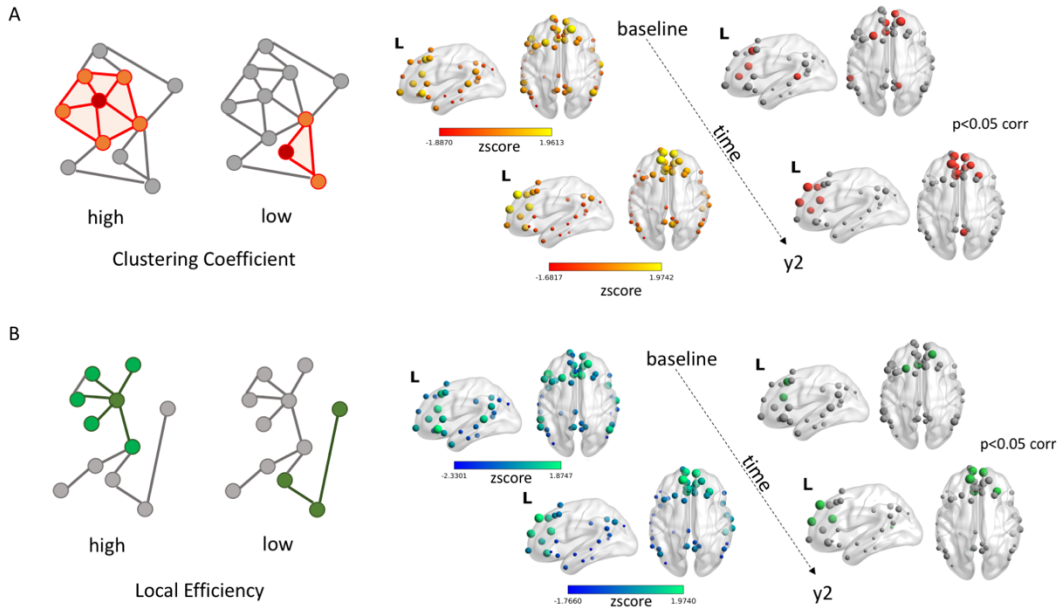

Figure 5. Topological differences between HC and MCI patients. Compared to HC, MCI patients showed significantly higher clustering coefficient (**A**) and local efficiency (**B**) values, especially over frontal nodes. After 2 years of time, the number of frontal nodes showing higher clustering coefficient/local efficiency in MCI patients increased, suggesting increased segregation over time. Nodes color and size is proportional to the z score values of clustering coefficient and local efficiency, respectively.

Finally, we tested if the nodes that at baseline showed higher clustering coefficient in the MCI population were also predictive of memory impairments at 2 years follow up. In this regard, the model resulted significant ($R^2 = 0.66$, $F_{(16)} = 3.84$, $p = 0.001$), with a significant negative correlation between the measure of clustering coefficient of a node in the right DMPFC (coordinates [16 46 44]) and DCBs' N1 - probability of encoding into the durable learned state ($\beta = -0.56$, $p = 0.006$) (see Figure 6A). Baseline scores were also observed

to be a significant predictor of memory performance 2 years after ($\beta = 0.75$, $p = 0.0002$) (see Figure 6B). When the same model was run to test the power of DMN nodes' local efficiency in predicting memory performance a 2 years follow-up, no significant association was observed ($R^2 = 0.25$, $F_{(20)} = 1.71$, $p = 0.18$).

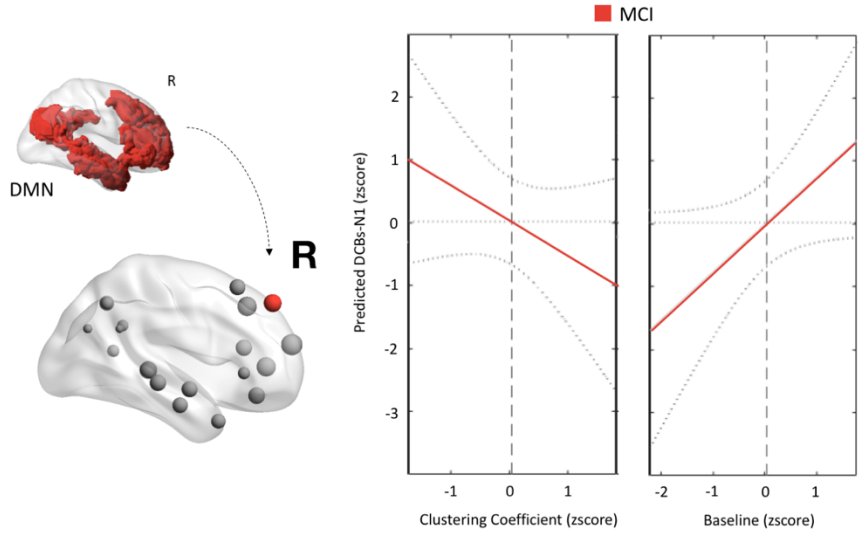

Figure 6. Topological predictors of future memory impairment at the single node level. **A**. In MCI patients, the clustering coefficient of one DMN node in the right dorsomedial prefrontal cortex (marked in red) significantly predicted a decrease in memory performance after 2 years. **B**. The same model also predicted a positive correlation between scores collected at baseline and after 2 years.

3. Discussion

In this study, we tested if functional abnormalities within two large brain networks, the DMN and the FPN, could be predictive of memory impairments after two years. We investigated brain connectivity through graph theory, hypothesizing that a loss in the efficiency of information transfer within these networks may occur some time before the

onset of clinical symptoms, therefore constituting an early biomarker of MCI-to-AD progression. Graph theory represents a methodological advantage compared to traditional approaches, as complex systems- including the brain- subserve to universal optimization laws, which guarantee easier generalizability and interpretability of findings (Bassett et al., 2010; Bullmore & Bassett, 2011). As a result, the study of the brain as a graph becomes particularly useful when we wish to study any deviance from the norm of a pathological brain (Farahani et al., 2019). As the efficiency in the global and local processing of information is driven by where, along a continuum, the individual brain collocates in terms of wiring costs and structured organization, in this study we decided to look for alterations in both *integration* and *segregation* mechanisms. Indeed, the extensive FC changes observed in AD have given it a definition as a disconnection syndrome (Delbeuck et al., 2003; delEtoile & Adeli, 2017). For instance, the brain graph of AD patients has been observed to be characterized by less interconnectivity and more segregated clusters than that of healthy controls (Çiftçi, 2011), with a decreased inter-regional connectivity typically reported over posterior cortices (Sanz-Arigita et al., 2010). This is often counterbalanced by an increased intra-regional connectivity over prefrontal areas (Sanz-Arigita et al., 2010), implying the presence of a compensatory mechanism (Hillary et al., 2015; Suckling et al., 2015), making the poster-to-anterior disconnection one of the main key features of the AD brain (Wang et al., 2007). Although less marked, some studies suggest that similar alterations might be visible since the earlier stages of MCI (Badhwar et al., 2017). Still, we lack a more specific understanding on how these patterns of hypo- and hyper-connectivity might be responsible for the earliest clinical symptoms that usually bring the individual under clinical attention, i.e., the emergence of episodic memory pitfalls. We aimed to fill this gap in the present study, which not only

strictly focuses on patients at prodromal stages, for which boosting interventions might still be possible, but also relies on a unique battery of data specifically aimed at investigating the steps-by-steps of memory encoding, consolidation and retrieval to disentangle where susceptibilities might emerge as a function of pathology. Furthermore, we aimed to do so in a proactive manner, trying to predict the emergence of memory weaknesses 2 years in advance based on the individual brain topology at baseline.

From a general point of view, our results are consistent with prior findings in the literature. For instance, we observed distinguishable DMN topography features between HC and MCI, characterized by significantly greater segregation of this network (higher clustering coefficient and local efficiency) in MCI patients. When broken down at the single node level, we observed that this higher clustering coefficient/ local efficiency was mainly imputable to its frontal nodes. Importantly, this distribution was even more marked at 2 years follow-up compared to baseline, suggesting a progressive segregation pattern as a function of time and, presumably, pathology. As both graph measures reflect the tendency of a node to have a greater distribution of connections within neighboring nodes, and hence to share information transfer "locally", these results are in line with the previously reported greater connectivity within frontal areas in MCI/AD (Chandra et al., 2019; Wang et al., 2007). Generally, this has been interpreted as evidence of compensatory mechanisms, which would operate by increasing the FC in prefrontal regions to counteract the loss of connectivity between regions (Wang et al., 2007). When put in relation to episodic memory performance, as we did in this study, we observed a significant group effect in the relationship between DMN clustering coefficient and the probability of encoding into a durably learned state (DCBs' N1 score), as well as the probability of retrieving from the durably learned state after a 5-minute delay with

distraction (DCBs' R3 score). In particular, a positive association was observed between DMN clustering coefficient and memory encoding at 2 years in HC. On the other hand, at the nodes' level analysis, MCI patients showed a negative association between the clustering coefficient of the right dorsomedial prefrontal cortex and efficient memory encoding after 2 years. Our interpretation is that, in HC, the easier the information transfer between DMN nodes, the higher the chances of correct episodic memory encoding. On the other hand, MCI patients present a greater recruitment of the same regions whilst showing a poorer performance. One possible interpretation is that compensatory mechanisms in the MCI brain result in greater functional costs with little behavioral benefit, such as that the individuals that at baseline already show a higher tendency of processing information locally within frontal areas, rather than more widely, will present greater encoding difficulties in the next 2 years. These patients might be the ones at higher risk of receiving a diagnosis of AD within the same time window. In the lack of task-evoked activity fMRI data, our interpretation of the results as evidence of compensatory mechanisms can only be speculative, although in line with prior evidence in the literature (Hillary et al., 2015; Suckling et al., 2015; Wang et al., 2018). A secondary possible explanation for our findings has been given by different studies reporting hyperconnectivity as a common response to neurological disruption, and therefore occurring in various set of conditions, such as MCI, AD, but also traumatic brain injury or multiple sclerosis (Hillary et al., 2015). Frontal hyperconnectivity would occur in in combination of connectivity gain and loss withing networks and it would provide the minimum resources required to meet task demands (Hillary et al., 2015). Moreover, another study using fMRI has reported a parametric relationship between the continuous high baseline activity of regions and hubs in the DMN, especially frontal ones, and

amyloid deposition (Buckner et al., 2009), therefore suggesting that the hyperconnection found in frontal regions of MCI patients may be also interpreted as a maker of early diffusion of amyloid in the isocortex and hence as a marker of progression to AD (Buckner et al., 2009). Finally, our results indicating a possible involvement of the right dorsomedial prefrontal cortex during encoding of information may seem to be counterintuitive with regard to HERA model, for witch, in memory performances, left prefrontal areas are the ones selectively implicated (Habib et al., 2003). However, our findings may be explained in light of the HAROLD model, since a decrease in hemispheric asymmetry could account for the supplementary implication of right frontal regions (Cabeza, 2002).

In support of the compensatory hypothesis, one possible contributor to such compensation mechanisms is the individual level of cognitive reserve, explained as the individual ability to show resilience and/or efficient compensation in face of pathology thanks to fitter brain patterns resulting from a life of engaging into cognitively stimulating activities and healthy lifestyles (Wang et al., 2007). In our study, all participants had high levels of education (HC: mean = 16.6±2.1; MCI: 15.7±2.3), which represents the most informative and used proxy in the computation of reserve estimates (Barulli & Stern, 2013). Although the lack of variability in this metric prevents us from analyzing the effect that interindividual differences in reserve might have in shaping the observed relationship between DMN frontal segregation and encoding of episodic memory, it also augments the strength and predictive power of our measures. Indeed, patients with high levels of reserve can usually compensate better and for longer the cognitive dysfunctions caused by AD, for example through the use of alternative strategies to help them overcome the initial memory pitfalls (e.g. spontaneously using agendas or other memory aids) (Andel

et al., 2006; Bruandet et al., 2008; Menardi et al., 2018) However, this also often results in a delayed diagnosis of AD, when the underlying pathology has already reached a much more advanced stage compared to patients with lower cognitive reserve (Andel et al., 2006; Bruandet et al., 2008; Menardi et al., 2018). Here, we prove that increased DMN clustering (especially of its frontal nodes) is predictive of memory decline in individuals with high reserve, suggesting a possible early detection of patients at risk of developing AD and that often go undiagnosed. This represents a crucial aspect, as today's aging population is characterized by higher education compared to past generations (Burger & Mortimer, 2021; Mortimer et al., 2020), which brings the need to develop more sensitive tools. This interpretation is given from a qualitative perspective on our hand and future studies should be conducted to test this hypothesis, for example by including individuals with lower levels of reserve to observe if distinguishable patterns can be observed.

In this study, models' goodness in revealing an association between topography and behavior was also made possible by the use of a highly specific episodic memory assessment tool, the DCBs (Bock et al., 2022), which might provide greater sensitivity than global scales. Indeed, averaging the performance across encoding, retrieval and recall mechanisms might otherwise hinder early and more subtle impediments at specific stages. In particular, our results highlight that episodic memory impairments in MCI patients might particularly evolve around the encoding of relevant event features constituting the episodic memory. On the other hand, we were not able to predict changes in more general global cognitive scales, such as the ADAS-Cog, which provide more approximate and less sensitive indices of cognitive decline.

Another contribution of the present study is that it highlights the role of prefrontal cortices in episodic memory impairments more (and probably earlier) than temporal regions,

which are the brain areas traditionally associated with memory difficulties in AD. Indeed, in typical AD, the emerge of symptoms follows a sequential order (episodic memory loss→ semantic memory loss → aphasic, apraxic, and visuospatial symptoms → motor and visual deficits) which mirrors neuronal loss due to atrophy (MTL (especially hippocampus) → posterior cingulate cortex → frontal and parietal cortices → sensorimotor and occipital cortex) (Talwar et al., 2021). Here, we show that the earliest biomarker of future episodic memory impairments in MCI patients might instead be the functional clusterization of DMN's frontal regions. With regard to the compensatory hypothesis, this is possibly due to the fact that functional compensatory mechanisms might be the more prominent feature of the pathology at its prodromal stages, when neural loss in the MTL is still only at the beginning. Hence, whilst temporal cortices still show activity patterns similar to normal aging since atrophy of these regions might have not yet reach a critical stage, frontal cortices might show an earlier neurocompensatory role in trying to maintain cognitive efficiency (Wang et al., 2018), representing an early stressor. Unfortunately, the computation of gray matter estimates fell beyond the scope of this study, but our interpretation suggests an important link between cortical atrophy over posterior DMN regions and a counteracting increased connectivity over its frontal component. Distinct functional alterations between anterior and posterior components of the DMN have indeed been recently proved (Yang et al., 2023). It is also important to highlight that in this study, the frontal involvement was indeed within regions belonging to the DMN rather than the FPN. For the latter, we still observed a positive correlation between its degree of clustering coefficient and the probability of encoding, this time into a transiently learned state (DCBs- N2 scores). This significant association between main effects in the model was observed across thresholds, but the models per se did not reach

statistical significance. We hypothesize that this might represent a trend in the data but that the somehow limited sample size of the current study might have limited the strength of the model.

4. Conclusions

The present study highlights the role of DMN topological alterations, especially in terms of increased segregation in the information processing of its frontal components, as an early biomarker of cognitive worsening in episodic memory encoding. In particular, the study emphasizes that functional compensatory mechanisms in prefrontal regions might be a more prominent feature of the pathology at its prodromal stages, representing an early stressor. These findings might be potentially useful in the early detection of patients at higher risk of clinical progression and for whom resilience boosting interventions might still be put in place.

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6. Appendix I

DCBs: Networks results at different thresholds

DMN

Encoding

80%

Significative interaction term ($R^2 = 0.474$, $F_{(38)} = 3.11$) between clustering coefficient and group a 80% threshold ($\beta = -1.06$, $p = 0.01$).

Interaction between baseline and group at 80% threshold ($R^2 = 0.474$, $F_{(38)} = 3.11$, $p = 0.0045$, $\beta = 0.6$, $p = 0.01$).

70%

Significative interaction ($R^2 = 0.543$, $F_{(39)} = 4.07$, $p = 0.0005$) between baseline and group at 70% threshold ($\beta = 0.5$, $p = 0.01$).

60%

Significative interaction ($R^2 = 0.478$, $F_{(40)} = 43.32$, $p = 0.003$) between baseline and group at 60% threshold ($\beta = 0.5$, $p = 0.02$).

Retrieval

70%

Significative positive correlation ($R^2 = 0.414$, $F_{(41)} = 2.63$, $p = 0.012$) between the measure of local efficiency and scores obtained at DCBs' R3 at 70% threshold ($\beta = -1.06$, $p = 0.008$).

60%

Significative positive correlation ($R^2 = 0.428$, $F_{(41)} = 2.79$, $p = 0.01$) between the measure of local efficiency and scores obtained at DCBs' R3 at 60% threshold ($\beta = 0.5$, $p = 0.008$).

FPN

Encoding

70%

Significative positive correlation ($R^2 = 0.277$, $F_{(40)} = 1.4$, $p = 0.212$) between the measure of clustering coefficient and scores obtained at DCBs' N2- probability of encoding into the transiently learned state at 70% threshold ($\beta = -1.69$, $p = 0.006$).

60%

Significative positive correlation ($R^2 = 0.202$, $F_{(41)} = 0.946$, $p = 0.509$) between the measure of clustering coefficient and scores obtained at DCBs' N2- probability of encoding into the transiently learned state at 60% threshold ($\beta = -1.7349$, $p = 0.01$).