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# Enhanced resting-state functional connectivity between core memory-task activation peaks is associated with memory impairment in MCI

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ABSTRACT

Resting-state functional connectivity (FC) is altered in Alzheimer's disease (AD) but its predictive value for episodic memory impairment is debated. Here, we aimed to assess whether resting-state FC in core brain regions activated during memory-task functional magnetic resonance imaging is altered and predictive of memory performance in AD and amnestic mild cognitive impairment (aMCI). Twenty-three elderly cognitively healthy controls (HC), 76 aMCI subjects, and 19 AD dementia patients were included. We computed resting-state FC between 18 meta-analytically determined peak coordinates of brain activation during successful memory retrieval. Higher FC between the parahippocampus, parietal cortex, and the middle frontal gyrus was observed in both AD and mild cognitive impairment compared to HC (false-discovery rate—corrected $p < 0.05$). The increase in FC between the parahippocampus and middle frontal gyrus was associated with reduced episodic memory in aMCI, independent of amyloid-beta positron emission tomography binding and apolipoprotein E ε4-carrier status. In conclusion, increased parahippocampal-prefrontal FC is predictive of impaired episodic memory in aMCI and may reflect a dysfunctional change within the episodic memory–related neural network.



## 1. Introduction

Studies including resting-state functional magnetic resonance imaging (fMRI) have revealed large-scale functional networks in the human brain. Such resting-state networks show high functional connectivity (FC), that is, a synchronization of spontaneous low-frequency fluctuations in brain activity between different brain regions. Because resting-state fMRI is acquired without engaging the subjects in a particular cognitive task (i.e., during rest), resting-state FC can be considered a measure of basic activity of intrinsic functional networks in the brain (Smith et al., 2009). In Alzheimer's disease (AD), altered FC in resting-state networks has been reported across the spectrum of clinical severity including elderly cognitively normal subjects with increased levels of amyloid burden, amnestic mild cognitive impairment (aMCI), and dementia (Greicius et al., 2004; Hedden et al., 2009; Sorg et al., 2007). Such abnormalities of FC were detected in AD even when controlling for gray matter atrophy (Agosta et al., 2012; Sorg et al., 2007; Wang et al., 2013). Together, these results suggest that alterations of FC in resting-state networks are an independent, early brain change in the course of AD.

The functional implications of such resting-state FC changes are debated (for review see Pievani et al., 2014). Resting-state fMRI makes no task demands to the patient, which has advantages for clinical practice. In the present study, we aimed to identify resting-state network changes that are associated with episodic memory impairment in aMCI. The rationale for using resting-state FC as a predictor of memory performance comes from the known spatial

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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overlap between resting-state networks and task-related networks for cognitive functions (Li et al., 2015; Smith et al., 2009; Yeo et al., 2011). The activity of resting-state networks is modulated during tasks, suggesting that resting-state networks are the building blocks of task-related brain activation underlying cognitive performance (Li et al., 2015).

In AD, the resting-state network that is most prominently affected is the default mode network (DMN). This network includes several brain regions known to be involved in episodic memory retrieval such as the posterior cingulate and hippocampus (Huijbers et al., 2012). A reduction of FC within the DMN has been observed in preclinical AD, aMCI, and dementia (Greicius et al., 2004; Hedden et al., 2009; Wang et al., 2013) and was found to be associated with lower episodic memory performance (Wang et al., 2013). Deficits in episodic memory have further been associated with increased FC in the hippocampus of aMCI and AD patients (Pasquini et al., 2014; Wang et al., 2013). However, several studies failed to reveal an association between FC in the DMN and memory impairment in AD or aMCI (Agosta et al., 2012; Binnewijzend et al., 2012).

To understand which resting-state FC changes are related to episodic memory performance, brain regions other than the DMN need to be taken into account. Areas commonly activated during memory encoding or retrieval are distributed across several of the "classic" resting-state networks (Li et al., 2015), suggesting that brain activity underlying episodic memory is not confined to any single network (Damoiseaux et al., 2006). For example, a recent resting-state fMRI study showed that resting-state FC between different resting-state networks such as the DMN, cingular-opercular network, and the frontoparietal attention network was associated with memory performance in cognitively healthy subjects (Geerligs et al., 2015).

In the present study, we mapped the number of connections and the strength of resting-state FC between meta-analytically determined hotspots of brain activation observed during successful memory retrieval (Spaniol et al., 2009). The aims of the present study were to test whether FC between these core brain regions (1) can be observed during rest, (2) is altered in aMCI and AD, and (3) is predictive of episodic memory impairment as assessed by standard neuropsychological tests.

## 2. Methods

### 2.1. Participants

All subjects were recruited within the Alzheimer's Disease Neuroimaging Initiative (ADNI, phase GO and II, www.loni.ucla.edu/ADNI; Weiner et al., 2013). For the present study, we included a total of 23 elderly cognitively healthy controls (HC), 76 subjects with aMCI and 19 AD. The selection criteria were the availability of resting-state fMRI, T1-weighted MRI, AV45-positron emission tomography (PET), and a memory composite score (Crane et al., 2012; Supplementary Fig. 1). HC subjects were required to show low global levels of AV45-PET binding (standardized uptake value ratio $<1.11$, A$\beta-$) to yield a control group with low probability of AD pathology. In ADNI, the general inclusion criteria were: age between 50 and 90 years, modified Hachinski score $\leq 4$, education of at least 6 grade level, and stable treatment of at least 4 weeks in case of treatment with permitted medication.

ADNI is a longitudinal multicenter study started in 2003 in North America as a public private partnership to investigate neuropsychological parameters, neuroimaging features, and other biomarker for tracking and predicting AD-related cerebral and cognitive changes (see Supplementary Method). Ethical approval was obtained by the ADNI investigators (http://www.adni-info.org/pdfs/adni_protocol_9_19_08.pdf). This study was approved by the institutional review boards of all the participating institutions.

### 2.2. Episodic memory performance

Episodic memory ability was quantified by a composite score (ADNI-memory) based on subcomponents of common neuropsychological tests including the Rey Auditory Verbal Learning Test (word list learning trials, recall, and recognition), Mini-Mental State Examination (word recall), Alzheimer's Disease Assessment Scale (ADAS, word list learning, recall, and recognition) and Logical Memory I and II, as previously described (Crane et al., 2012). The composite scores were downloaded from the ADNI web page (http://adni.loniucla.edu/).

### 2.3. MRI acquisition

All MRI data were acquired on 3T Philips systems. For rsfMRI, subjects were instructed to keep their eyes open, the following acquisition parameters were used: single shot T2*-weighted echo planer imaging pulse sequence in transverse slice orientation, with repetition time/echo time = 3000/30 ms, flip angle = 80°, 3.3 mm isotropic spatial resolution with 48 slices, with voxel size of $3.31 \times 3.31 \times 3.31$, matrix size of $64 \times 59$, and 140 volumes (for more detail refer to the MRI Training Manual, http://adni.loni.usc.edu/).

### 2.4. fMRI preprocessing

The first 10 volumes were discarded to ensure steady-state magnetization. The remaining volumes were realigned to correct for head motion. The realigned volumes were registered to the subject's T1-weighted MRI image and high-dimensionally normalized to MNI standard space (see Supplementary Method). The images were adjusted for the realignment parameters and the mean time courses of blood-oxygen-level dependent signal changes within the white matter and grey matter (GM). The images were smoothed (full width at half maximum 6 mm), detrended, and band-pass filtered between 0.01 and 0.08 Hz (see also Supplementary Method for more details).

### 2.5. Placement of regions of interest

We computed the FC between regions of interest (ROI) of the putative episodic memory network. ROIs were placed according to a previously published voxelwise activation likelihood estimation meta-analysis of 30 published fMRI studies on episodic memory, including 478 cognitively healthy adults (Spaniol et al., 2009). The meta-analysis yielded 18 peak coordinates of brain activation associated with successful memory retrieval on forced choice recognition tasks (Spaniol et al., 2009). The spatial coordinates were converted from Tailarach space to the MNI standard space using the Lancaster transform (Lancaster et al., 2007). Spherical ROIs (radius 6 mm) were created around each of the peak coordinates in MNI space, using FSL (v.5; http://fsl.fmrib.ox.ac.uk/fsl). The MNI coordinates of each ROI are listed in Supplementary Table 1 and the location in the brain is displayed in Supplementary Fig. 2. The mean time course within each ROI was calculated for ROI-to-ROI FC analysis. To assess whether partial volume effects may influence the results, we also obtained GM volume within the ROIs. ROI GM volume was estimated based on the spatially normalized and modulated gray matter maps, where the same spatial normalization parameters were used that had also been applied to the resting-state fMRI scans for spatial normalization to the MNI space.

### 2.6. Statistical analysis

The ROI-to-ROI FC analysis was performed with the Conn toolbox v. 13.p based on MATLAB (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon, 2012). The strength of FC was determined via pairwise Pearson-moment correlations between the mean time courses of the ROIs, resulting in a 18 × 18 matrix of FC values which were Fisher z-score transformed. To test the number of significant connections between the ROIs in each group, we computed one-sample $t$ tests for each pairwise ROI-to-ROI FC value within each group (false discovery rate (FDR) corrected at $p = 0.05$, n = 153). Differences in the number of significant connections between groups were computed via 2-sample $t$ tests.

To select potential predictors of episodic memory performance among the high number of ROI-to-ROI values, we applied the following 2-step procedure. In the first step, we tested for which ROI-to-ROI connections the strength of FC was abnormally changed in AD dementia subjects compared to HC subjects. To this end, we applied analyses of covariance (ANCOVAs) including diagnosis (HC vs. AD), age, gender, and education as independent variables (training sample). The $p$-value for each ANCOVA was FDR-corrected at $p < 0.05$ (for n = 153 multiple comparisons). In the second step, the strength of FC of those ROI-to-ROI connections that were found significantly altered in the AD dementia group was tested as predictors of episodic memory performance in the aMCI group. We computed linear regression models including episodic memory score as the dependent variable and strength of FC, age, gender, education, and MMSE as independent variables. For exploratory reasons, we compared the strength of FC values among all groups including HC, aMCI, and AD. To this end, we used ANCOVA, with diagnosis as a factor and age, gender, and education as covariates. Simple main effects of diagnosis were followed up by Fisher's least significance difference post hoc test for pairwise group comparisons, FDR-corrected at $p = 0.05$.

All group-level statistical analyses were done with the stats package of statistical software R implemented in R Studio v. 0.98.501 (Boston, MA, http://www.rstudio.com/).

## 3. Results

Neuropsychological and demographic summary statistics for each diagnostic group are provided in Table 1.

**Table 1**
Characteristics of each diagnostic group

| Variable | HC | MCI | AD |
|---|---|---|---|
| N | 23 | 76 | 19 |
| Gender (F/M) | 16/7 | 36/40 | 10/9 |
| Age (y) | 74.8 [6.4] | 71.0 [7.5][a*] | 73.6 [6.9] |
| AV45-PET | 1.0 [0.1] | 1.2 [0.2][a***] | 1.4 [0.2][a,b***] |
| APOE ε4 (+/−) | 5/18 | 34/42 | 16/1[a,b***] |
| Education | 15.8 [2.1] | 16.4 [2.6] | 15.7 [2.4] |
| MMSE | 28.8 [1.4] | 27.9 [1.8][a***] | 23.3 [2.6][a,b***] |
| ADAS-Cog | 6.4 [3.3] | 9.2 [4.1][a**] | 20.0 [5.8][a,b***] |
| Composite episodic memory score[c] | 0.8 [0.5] | 0.3 [0.5][a**] | −0.6 [0.6][a,b***] |

Values represent the mean [standard deviation] or number of subjects. Two AD subjects had no APOE4 value.
Key: AD, Alzheimer's disease with dementia; ADAS-Cog, Alzheimer's Disease Assessment Scale- Cognitive Subscale; APOE, apolipoprotein E; APOE ε4+, APOE ε4-allele carrier; APOE ε4−, APOE ε4− allele noncarrier; F, female; HC, cognitively healthy; M, male; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N, number of subjects.
[a] Compared to HC.
[b] Compared to MCI. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
[c] Composite episodic memory score described previously (Crane et al., 2012).

### 3.1. Diagnostic group differences in FC

The network graphs for the HC and AD dementia group are displayed in Fig. 1A and C. The number of significant ROI-to-ROI connections was larger in the AD dementia group compared to HC ($t = 3.63$, $p < 0.001$). The network graphs of FC in aMCI are displayed in Fig. 1B. The number of significant ROI-to-ROI connections was larger in the aMCI group compared to HC ($t = 10.23$, $p < 0.001$) or AD dementia ($t = 5.87$, $p < 0.001$).

The AD dementia group showed increased strength of FC for 4 ROI-to-ROI connections compared to HC (Fig. 2). The pairs of ROIs included connections between the left middle frontal gyrus (MFG) and the right superior parietal gyrus (SP) or angular gyrus (AG), and connections between the right MFG and the left parahippocampal gyrus (PHC) or caudate (CD). There were no reductions of FC in AD dementia compared to HC.

Exploratory analysis of all ROI-to-ROI connections (N = 153) revealed no additional FC alterations in aMCI other than those found altered in AD dementia.

As displayed in Fig. 3, the strength of FC in aMCI was intermediate between that for HC and AD for each of the 4 connections. Results of the ANCOVAs showed significant group differences for each of the 4 connections, including the MFG-PHC ($F = 5.64$, $p < 0.01$), MFG−SP ($F = 8.33$, $p < 0.001$), MFG-AG ($F = 14.5$, $p < 0.001$), and MFG-CD ($F = 9.36$, $p < 0.001$). Fisher's least significance difference post hoc tests, with FDR-corrected $p$-values, showed that for each connection the group difference in FC followed the pattern AD > aMCI > HC.

To test whether GM volume changes are a potentially confounding variable, we tested the correlation between the ROI gray matter volume and ROI FC. Results of the Pearson-moment correlation analysis showed no significant association for any of the 4 connections, when tested within each diagnostic group or across all subjects (FDR-corrected $p > 0.05$).

### 3.2. Association between changes in the strength of FC and memory performance in MCI

Focusing on the 4 connections for which the strength of FC was found to be increased in aMCI and AD dementia, we found higher strength of FC between the right MFG and the PHC to be associated with reduced episodic memory performance in aMCI [$t(70) = -2.14$, $p = 0.04$, $r^2 = 0.36$, FDR-corrected $p = 0.06$, Fig. 4]. We computed the diagnosis (HC, aMCI, AD dementia) × FC interaction, controlled for age, gender, and education to predict episodic memory. The results showed that the slopes of FC in HC differed significantly from those in aMCI ($\beta = -1.03$, $p = 0.007$) or AD dementia ($\beta = -1.71$, $p = 0.001$). None of the other 3 connections showed associations between the strength of FC and episodic memory scores.

For exploratory reasons, we also examined associations between the strength of FC in the MFG-PHC connection and memory performance in the HC dementia and AD group (training set). There was an association between higher strength of FC in the MFG-PHC connection and lower episodic memory score in the AD group ($p = 0.04$) but not in the HC group ($p = 0.1$). Next, we included GM volume of the FC ROIs as an additional covariate in the regression model, using stepwise backward selection to control for any effects of gray matter atrophy. For the MFG-PHC connection, FC remained a significant predictor of episodic memory in the aMCI and AD groups.

### 3.3. FC and elevated levels of AV-45 PET in aMCI

Forty-four aMCI subjects showed abnormally high global AV45-PET binding (SUVR >1.11, aMCI Aβ+) and 32 aMCI showed

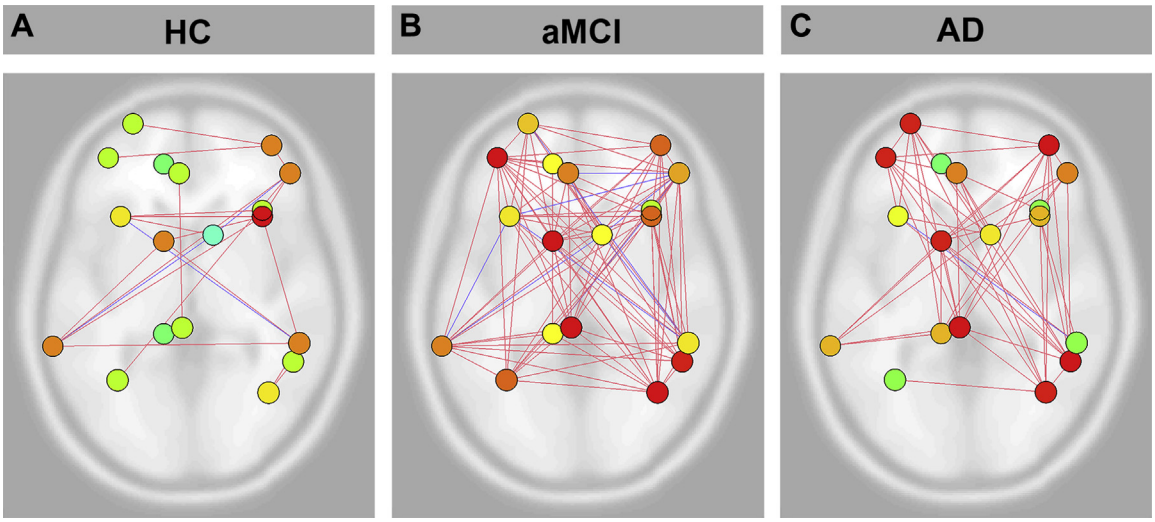


**Fig. 1.** Functional connectivity between regions of interest (ROIs) of the episodic memory network for HC (A), MCI (B), and AD dementia (C). Red lines and blue lines refer to positive and anticorrelations. *p* values of significant connections are FDR adjusted below 5%, corrected for the 153 connections between each pair of ROIs. ROI color corresponds to the number of connections to (or from) each ROI. Abbreviations: AD, Alzheimer's disease with dementia; aMCI, amnestic mild cognitive impairment; FDR, false-discovery rate; HC, cognitively healthy. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

normal levels of AV45-PET binding (SUVR <1.11, aMCI Aβ−). To determine whether FC changes in aMCI are related to abnormal Aβ deposition, we compared the strength of FC of each of the 4 connections between aMCI Aβ+ and aMCI Aβ− subgroups. There was no indication of a difference in the strength of FC between the Aβ groups for any of the 4 connections, including those between the left MFG and the right SP ($F = 0.51$, $p = 0.48$) or AG ($F = 0.68$, $p = 0.41$) and between the right MFG and the left PHC ($F = 0.48$, $p = 0.49$) or CD ($F = 0.24$, $p = 0.63$), suggesting that the increase in FC in the aMCI group was not associated with the levels of Aβ. To test the influence of Aβ status on the association between FC (MFG vs. PHC) and memory, we repeated the ANCOVA, this time testing the interaction term diagnosis (HC, MCI Aβ−, aMCI Aβ+, AD dementia) × FC to predict episodic memory. Results showed that the interaction term was significant, where the slope of FC differed between HC compared to MCI Aβ− ($\beta = -1.28$, $p = 0.004$), aMCI Aβ+ ($\beta = -0.89$, $p = 0.03$), and AD dementia ($\beta = -1.71$, $p = 0.0005$, Supplementary Fig. 3). However, the slopes of FC did not differ between the aMCI subgroups and AD ($p > 0.05$).

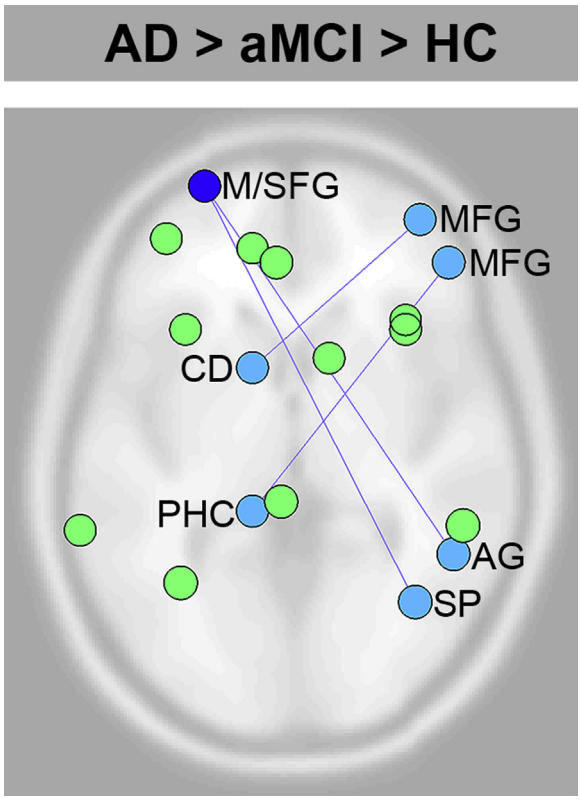


**Fig. 2.** Spatial projection of ROI-to-ROI connections onto an axial brain slice. The strength of FC was increased in AD dementia compared to the strength of FC in MCI which in turn was larger than the strength of FC in HC. ROI color corresponds to the number of connections to (or from) each ROI. Abbreviations: AD, Alzheimer's disease with dementia; AG, angular gyrus; aMCI, amnestic mild cognitive impairment; CD, caudate; FC, functional connectivity; HC, cognitively healthy; M/SFG, middle/superior frontal gyrus; MFG, middle frontal gyrus; PHC, parahippocampal gyrus; ROI, region of interest; SP, superior parietal. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

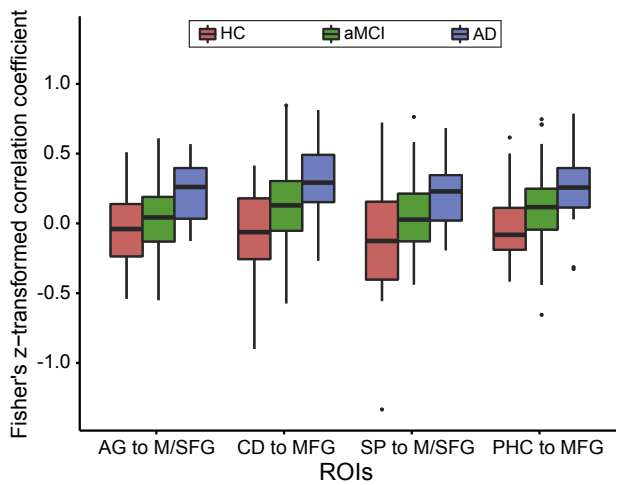


**Fig. 3.** Boxplot of functional connectivity values as a function of diagnosis on the 4 connections which significantly increased between HC and AD. Abbreviations: AD, Alzheimer's disease with dementia; AG, angular gyrus; aMCI, amnestic mild cognitive impairment; CD, caudate; HC, cognitively healthy; M/SFG, middle/superior frontal gyrus; MFG, middle frontal gyrus; PHC, parahippocampal; ROIs, regions of interest; SP, superior parietal.

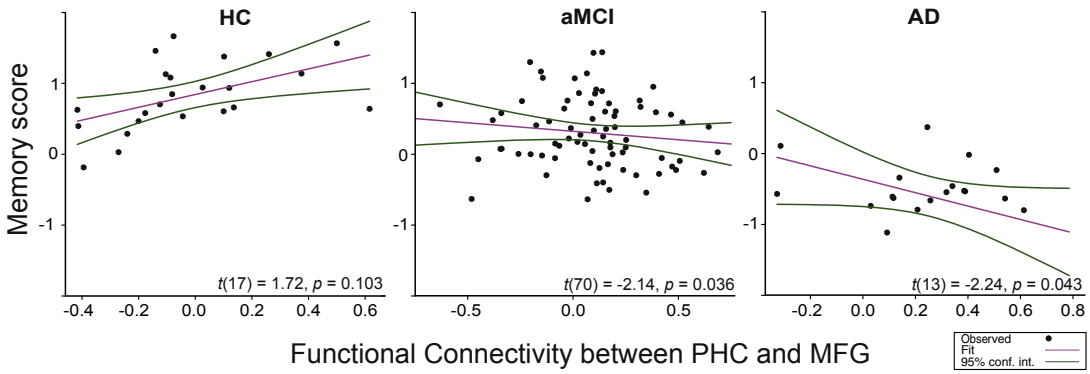


**Fig. 4.** Regression plot of the association between FC PHC-MFG connection and episodic memory composite scores for each diagnostic group including HC, aMCI, and AD dementia. Abbreviations: AD, Alzheimer's disease with dementia; aMCI, amnestic mild cognitive impairment; FC, functional connectivity; HC, cognitively healthy; MFG, middle frontal gyrus; PHC, parahippocampal.

## 4. Discussion

The first major finding of the present study was the increased strength and number of connections between peak locations of memory task–related brain activation in aMCI and AD dementia subjects compared to HC. The second major finding was that the abnormal increase in the strength of FC between the MFG and the PHC was associated with reduced episodic memory performance in aMCI and AD dementia.

The current finding of increased strength of FC in aMCI and AD is in line with previous reports of increased strength of FC between the hippocampus and the lateral prefrontal cortex (Wang et al., 2006). Those studies which explored FC changes within the whole brain in patients with AD dementia reported increased strength of FC within the frontoparietal and prefrontal resting-state network (Agosta et al., 2012) and increased strength of FC between widely distributed cortical ROIs (Gardini et al., 2015; Wang et al., 2007). In contrast, reduced resting-state FC in patients with MCI and AD was primarily confined to the DMN in previous studies (Agosta et al., 2012; Binnewijzend et al., 2012; Greicius et al., 2004). For the present study, the increase in the strength of FC was found exclusively for connections that were not confined to the DMN but spanned different functional clusters, that is, the connections were between the frontoparietal network (MFG ROI) and the posterior DMN (AG ROI), medial temporal lobe subsystem (parahippocampus), or a subcortical cluster (thalamus). In summary, these results suggest an increase in the strength of FC between brain regions that are typically activated during episodic memory retrieval across different resting-state networks in MCI and AD patients.

The second major finding showed that an abnormal increase in the strength of FC was associated with reduced episodic memory performance in aMCI. These findings are in agreement with previous reports of an association between increased local strength of FC within the hippocampus and lower episodic memory performance in AD dementia patients (Pasquini et al., 2014). In cognitively normal subjects, higher levels of interhemispheric FC between the hippocampi were associated with increased higher age and associated with faster memory decline (Salami et al., 2014). Here, we extended these findings by showing that the increased strength of FC between the hippocampus and lateral frontal cortex is associated with memory decline in aMCI. Task-related studies have shown elevated levels of hippocampus and parahippocampus activation in patients with aMCI (Dickerson et al., 2004, 2005). Higher abnormal increase in hippocampus activation was associated with faster subsequent cognitive decline in aMCI (Miller et al., 2008). Treatment of aMCI patients with an antiepileptic drug that reduced hippocampus hyperactivation lead to improved memory performance (Bakker et al., 2012). Together, these results suggest that hippocampus hyperactivity and the hyperconnectivity to brain areas involved in memory-related brain activation is detrimental to episodic memory performance in aMCI.

Results of a recent meta-analysis of resting-state fMRI studies suggested increased FC in brain areas such as the subcortical structures and the medial temporal and parietal lobe that occurred early in the course of AD (Jacobs et al., 2013). Increased activation of medial temporal lobe and parietal brain regions has also been observed in relation to memory task-fMRI, when tested in the preclinical and prodromal stage of AD (Celone et al., 2006; Sperling, et al., 2009, 2010). The question arises whether increased resting-state fMRI connectivity within the medial temporal lobe and other brain regions may constitute a candidate biomarker for the early detection of AD-related brain abnormalities (Jacobs et al., 2013). Compared to task-fMRI, resting-state fMRI is due to its task-free and relatively short assessment attractive for clinical application. Few studies, however, have tested resting-state fMRI for the detection of MCI or AD dementia (Bai et al., 2011; Dyrba et al., 2015; Wee et al., 2012), where resting-state fMRI connectivity measures alone stayed below a clinically relevant classification accuracy below 85%. For resting-state fMRI, feature selection, interindividual stability, and multicenter variability of FC are currently an intense area of research (Biswal et al., 2010; Feis et al., 2015) and may provide an important basis to increase the predictive accuracy of resting-state fMRI.

The underlying nature of the increase in FC in aMCI and AD is not known. One possible explanation is that increased brain activation results from increased deposition of Aβ. Previous studies showed that increased brain activity during memory task was associated with Aβ deposition in elderly cognitively healthy subjects (Elman et al., 2014) and aMCI patients (Huijbers et al., 2015). Results obtained in mice suggest that levels of Aβ are associated with epileptic spikes in neural activity, which may potentially explain increased neural activity in patients with AD. However, whether increased Aβ levels in the brain can also account for the increase in FC is questionable. If Aβ leads to aberrant neural activity, FC may not be increased, since FC requires the coordinated activity between different brain areas rather than a local increase in brain activity. In the present study, we did not find the observed increase in FC to be dependent on Aβ when tested in the aMCI subjects. These results suggest that increased levels of Aβ may not be necessary for the increase in FC in aMCI.

An alternative explanation is that the increase in FC reflects less efficient neural network activity. According to the dedifferentiation hypothesis, age-related changes in brain function lead to more diffuse brain activity due to less efficient neural processing (Dennis and Cabeza, 2011). Consistent with the dedifferentiation hypothesis, a study in elderly cognitively healthy subjects found an age-related decrease in modularity of resting-state FC within networks and increased inter-network connectivity (Geerligs et al., 2015). In the present study, we found not only increased strength of FC but also a higher number of connections in MCI and AD compared to HC. The number of connections peaked in MCI, being significantly higher compared to AD. It is possible that this increased density of the connections within the network may represent a more diffuse and less efficient processing. Less efficient neural processing may require increased FC, that is, a compensatory recruitment of additional neural resources to maintain task performance (Dickerson et al., 2004; Grady et al., 2003). Thus, the current finding of an inverse association between increased FC and memory performance may reflect a failed compensatory attempt (Bakker et al., 2012; Pasquini et al., 2014). However, a caveat of this interpretation is that the present study did not aim to assess efficiency of the network, and thus, no metric of efficiency or experimental manipulation of efficient processing was included. Therefore, this hypothesis requires confirmation in future studies.

It is important to acknowledge the potential limitations of our study. Increased levels of FC during resting-state FC provide only a snapshot of brain activity. During resting state, "spontaneous" brain activation is sampled without reference to external events and, thus, is inherently ambiguous to interpret. To alleviate this drawback, we attempted to tailor the study in a hypothesis-driven way, focusing on meta-analysis–derived brain regions that have previously been found to be activated during memory retrieval processes. However, a combined resting-state and memory task–related fMRI study design (Koch et al., 2014) is encouraged for future studies to investigate the association between rsfMRI and memory performance.

We also caution that the multisite acquisition of resting-state fMRI may have introduced between-site variability. In ADNI, fMRI scans, however, are acquired exclusively on Philips 3T MRI scanners, where standard resting-state fMRI sequences are applied across sites. Thus, such a study design may reduce the influence of major sources of interscanner variability. A statistical control or assessment of any intersite variability in the present study is almost impossible due to relatively high number of sites that contribute data.

Despite such drawbacks of resting-state fMRI, the current results on FC changes between core brain regions underlying episodic memory retrieval support the notion that resting-state fMRI provides a "window" to assess neural network function underlying cognitive performance. The present study provides an approach to design resting-state FC analysis to assess FC changes for predicting episodic memory impairment in MCI. FC is currently not established as a neuroimaging biomarker. Longitudinal studies to examine the value of FC for predicting future cognitive decline are needed.

## Disclosure statement

The authors have no conflicts of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.04.018.

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