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Basal functional connectivity within the anterior temporal network is associated with performance on declarative memory tasks

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ABSTRACT

Spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal, as measured by functional magnetic resonance imaging (fMRI) at rest, exhibit a temporally coherent activity thought to reflect functionally relevant networks. Antero-mesial temporal structures are the site of early pathological changes in Alzheimer's disease and have been shown to be critical for declarative memory. Our study aimed at exploring the functional impact of basal connectivity of an anterior temporal network (ATN) on declarative memory. A heterogeneous group of subjects with varying performance on tasks assessing memory was therefore selected, including healthy subjects and patients with isolated memory complaint, amnestic Mild Cognitive Impairment (aMCI) and mild Alzheimer's disease (AD). Using Independent Component Analysis on resting-state fMRI, we extracted a relevant anterior temporal network (ATN) composed of the perirhinal and entorhinal cortex, the hippocampal head, the amygdala and the lateral temporal cortex extending to the temporal pole. A default mode network and an executive-control network were also selected to serve as control networks. We first compared basal functional connectivity of the ATN between patients and control subjects. Relative to controls, patients exhibited significantly increased functional connectivity in the ATN during rest. Specifically, voxel-based analysis revealed an increase within the inferior and superior temporal gyrus and the uncus. In the patient group, positive correlations between averaged connectivity values of ATN and performance on anterograde and retrograde object-based memory tasks were observed, while no correlation was found with other evaluated cognitive measures. These correlations were specific to the ATN, as no correlation between performance on memory tasks and the other selected networks was found. Taken together, these findings provide evidence that basal connectivity inside the ATN network has a functional role in object-related, context-free memory. They also suggest that increased connectivity at rest within the ATN could reflect compensatory mechanisms that occur in response to early pathological insult.

Introduction

Over the past decade, an increasing number of studies have attempted to characterize neural networks using functional activation paradigms and, more recently, basal functional connectivity during resting state. Following the seminal work of Biswal et al. (1995), new post-processing methods such as independent component analysis (ICA) have emerged, which allow delineating several well-recognized and reproducible resting-state networks thought to reflect anatomo-functional systems (Beckmann et al., 2005; Cordes et al., 2000; Damoiseaux et al., 2006; De Luca et al., 2006; Fox et al., 2005; Fox et al., 2006; Fransson, 2005; Greicius et al., 2003; Lowe et al., 2008; Mantini et al., 2007; Salvador et al., 2005; van den Heuvel et al., 2008; van den Heuvel and Hulshoff Pol, 2010 for review; Varoquaux et al., 2010). This approach also provides evidence that specific networks are altered in the early stages of various diseases such as Alzheimer's disease (Greicius et al., 2004; Sorg et al., 2009).

Declarative memory refers to memory for personal events (episodic memory) and memory for facts and objects (semantic memory) (Kinsbourne and Wood, 1975; Moscovitch et al., 2006; Nadel and Moscovitch, 1997; Tulving, 1972). Declarative memory is highly dependent on the medial temporal lobe (MTL), a set of interconnected structures including the hippocampus and underlying

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entorhinal, perirhinal, and parahippocampal cortices. In a recent study, basal functional connectivity of the MTL was investigated using resting-state fMRI (Kahn et al., 2008). This study provided evidence for two separate brain networks involving distinct components of the MTL: i) a posterior network which includes the body of the hippocampus, the posterior parahippocampal cortex, along with the lateral parietal cortex, the posterior midline structures and the ventral medial prefrontal cortex; ii) an anterior network which is composed of the anterior hippocampus, the perirhinal/entorhinal cortices and the lateral temporal cortex extending into the temporal pole.

Several lines of evidence suggest that structures of the anterior temporal network (ATN) are precociously affected in Alzheimer's disease (AD), both anatomically and functionally. Neurofibrillary tangles initially develop in the anterior subhippocampal cortex (entorhinal and perirhinal cortex) before reaching the hippocampal formation (Braak and Braak, 1991; Delacourte et al., 1999). Structural neuroimaging studies also found early gray matter loss within subhippocampal structures (Barbeau et al., 2008; deToledo-Morrell et al., 2004; Du et al., 2001; Stoub et al., 2005; Xu et al., 2000), extending to anterior temporal regions (McDonald et al., 2009). Functionally, the different components of this ATN have been shown to be involved in some aspects of declarative memory. In particular, there is growing evidence that the perirhinal cortex plays a role in object-based recognition memory (Aggleton and Brown, 1999; Eichenbaum et al., 2007; Vargha-Khadem et al., 1997). Moreover, the anterior temporal lobes are known to be critical in the acquisition and maintenance of semantic knowledge (Hodges and Patterson, 1997; Lambon Ralph et al., 2009; Patterson et al., 2007; Visser et al., 2010). Consistently, patients with mild AD but also with amnestic Mild Cognitive Impairment (aMCI) exhibit retrograde semantic memory impairments (Hodges and Patterson, 1995; Joubert et al., 2010; Joubert et al., 2008), along with anterograde object-based recognition memory deficits (Barbeau et al., 2004a,b; Barbeau et al., 2008).

The present study focuses on basal functional connectivity of ATN and its impact on declarative memory performance. This issue was investigated in healthy subjects and a patient group that includes subjects with isolated memory complaints, aMCI and mild AD. The population is deliberately heterogeneous to constitute a continuum ranging from an objective impairment to normal performance on the assessment of memory. Basal connectivity of this selected ATN was first compared between patients and controls. Then, correlations between ATN and performance on memory tasks were evaluated. Moreover, in order to establish if relation of the ATN with memory is specific, we also studied correlations between performance on memory tasks and two additional networks, a default mode network and an executive-control network. Our prediction was that: i) basal functional connectivity within ATN would be altered in patients with memory deficits; ii) memory performance would correlate with basal functional connectivity of ATN; iii) memory performance would not correlate with the two additional networks.

Materials and methods

Subjects

Thirteen patients with differing degrees of memory impairment and twelve healthy controls matched for age, sex and educational level were included. All subjects gave informed consent to participate in the study, which was approved by the local Ethical Committee.

Patients and healthy controls underwent a full neurological examination, neuropsychological evaluation and a brain MRI exploration which included resting state fMRI. Patients were recruited from a memory clinic at the department of Neurology and Neuropsychology of the Timone Hospital in Marseille, France. They were classified into three groups on the basis of neuropsychological and neurological assessments. Memory complaint was evaluated with the intensity scale of memory complaint (EIPM), a 10 items home-made scale with a maximum score of 30 points. Normative data comes from a population of 105 healthy subjects (mean EIPM score, $m = 3.45 +/- 3$), 42 aMCI ($m = 16.26 +/- 3.77$) and 41 patients with an isolated memory complaint ($m = 17.07 +/- 3.22$). Among the thirteen patients, four were classified as mild AD, five as single domain aMCI and the remaining four as "memory complainers". Patients with AD met criteria for probable AD (McKhann et al., 1984) and had mild severity of dementia ($CDR = 1$; $MMSE = 22.5 +/- 1.7$; $EIPM = 13.5 +/- 4.79$). Patients with aMCI fulfilled Petersen's criteria of single domain amnestic MCI (Petersen et al., 2001), with a memory complaint, a performance of more than 1.5 SD below the mean of matched control subjects on a standardized memory task (the delayed free recall of the RL/RI 16, a French version of the Free and Cued Selective Reminding Test (Grober et al., 1988; Van Der Linden et al., 2004)), intact activities of daily living and no impairment in other cognitive domains such as language, visual perceptual and visual spatial skills or executive functions ($CDR = 0.5$; $MMSE = 26 +/- 1.41$; $EIPM = 12.4 +/- 4.2$). Finally, memory complainers exhibited a strong memory complaint but normal performance on cognitive testing ($CDR = 0$; $MMSE = 27 +/- 1.82$; $EIPM = 18 +/- 5.7$). All patients had no psychiatric disorder that could account for their memory disturbances (assessed by medical interview and the Hamilton rating scale for depression).

Healthy controls had no history of neurological and psychiatric disorder, no cognitive complaint, normal performance on neuropsychological assessment and no abnormal feature on structural brain MRI ($CDR = 0$; $MMSE = 29.41 +/- 1.08$; $EIPM = 2.5 +/- 1.5$).

Neuropsychological assessment

All subjects underwent an in-depth cognitive assessment. Three tasks were used to assess anterograde memory: i) The RL/RI 16, a French version of the Free and Cued Selective Reminding test (FCSR) (Grober et al., 1988; Van Der Linden et al., 2004), which requires the learning of sixteen unrelated words; ii) The Delayed Matching to Sample-48 items-test (DMS48), assessing object-based visual recognition memory (Barbeau et al., 2004b); iii) The Rey–Osterrieth complex figure (Rey, 1959). Two tasks were used to assess retrograde semantic memory: i) The Pyramid–Palm Trees Test (PPTT), a visual semantic matching task (Howard and Patterson, 1992); ii) The EVE 10 (Thomas-Anterion et al., 2006), evaluating knowledge of ten public events that occurred between 1950 and the early 2000s.

Executive skills were assessed with the Trail Making Test (Reitan, 1958) and several subtests of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 2000), including the matrix reasoning test, the digit span and digit-symbol coding subtests. Visuo-perceptual skills were evaluated with the Benton Facial Recognition Test (Benton, 1994).

Concerning performance on the assessment of memory, the following variables were retained for statistical analysis: delayed recall (free and total recall) and recognition at the RL/RI 16, delayed recognition at the DMS48, delayed recall at the Rey–Osterrieth complex figure, and scores at the PPTT and EVE 10 (total score). With regard to executive and visuo-perceptual functions, total raw scores were considered for analysis. The Trail Making test (TMT) is composed of two distinct sections, part A which provides a measure of psychomotor speed and sustained visual attention (the participant is asked to connect consecutive numbers displayed on a sheet of paper in the ascending order), and the part B which provides a measure of divided visual attention (the participant is asked to alternatively connect numbers and letters in ascending order). Performance is here expressed in terms of the time to complete each part of the test.

MRI procedures

Data acquisition

Imaging was performed on a 1.5T Magnetom Avanto MR Scanner (Siemens, Erlangen, Germany) equipped with a 32 channel head coil.

Foam padding and headphones were used to limit head motion and reduce scanner noise.

MRI sequences included 3D MPRAGE T1-weighted images (TE/TR 2.92 ms/1900 ms, 176 contiguous slices, 1 mm slice thickness, field of view (FOV) 256 mm, matrix 256) acquired in the sagittal plane.

Resting-state fMRI acquisition was composed of 200 brain volumes using single-shot GE-EPI sequence (TE/TR 50 ms/3300 ms; 36 contiguous slices, 3.5 mm thickness, matrix 64, FOV 225 mm) acquired during rest when subjects were instructed to keep their eyes closed and to stay awake with no precise thinking.

Data processing

Structural imaging. In order to obtain gray matter tissue probability maps to correct for atrophy on functional imaging analyses, 3D T1-weighted magnetic resonance images were post-processed using the VBM 5 toolbox implemented in SPM5 (Welcome Trust Centre for Neuroimaging, London, UK). Briefly, MRI data were spatially normalized, segmented to isolate the gray matter partition, and modulated. Resulting images, expressed as gray matter volume corrected for brain size, were masked (threshold: 60%) to remove remaining non-gray matter voxels and smoothed (FWHM 12 mm).

Functional imaging

Independent Component Analysis (ICA). Sources of spurious or regionally nonspecific variance related to physiological artifacts (CSF pulsations, head motions, etc.) were removed by regression including the signal averaged over the lateral ventricles, the signal averaged over a region centered in the deep cerebral white matter and the global brain signal to reduce the non-neuronal contributions to BOLD correlations (Bartels and Zeki, 2005; Bettus et al., 2009; Vincent et al., 2006). The MELODIC toolbox of FSL was used to perform a concatenated group Independent Component Analysis (ICA) used to extract 24 different resting state networks (RSN), including the predefined RSN described in previous works (Mantini et al., 2007; van den Heuvel and Hulshoff Pol, 2010 for review; Varoquaux et al., 2010). Images were corrected for acquisition delays (slice timing), realigned before spatial normalization (nonlinear registration) and smoothed (FWHM 12 mm). This data driven method allows for the extraction of distinct spatio-temporal patterns by identifying spatially independent and temporally synchronous brain regions (Calhoun and Adali, 2006). Out of these 24 independent components (ICs), we selected, upon visual inspection, three components corresponding to the ATN. A template of the anterior temporal network, as previously found in healthy controls (Kahn et al., 2008), was built using the WFU Pick-atlas toolbox (SPM5) including hippocampus, temporal pole, uncus and the enthorinal/perirhinal cortices. Then, out of the three temporal ICs, we selected the IC exhibiting the best spatial fitting with the mask by determining the numbers of pixels that were common to the two masks.

The same procedure was applied to select a default mode network based on a posterior cingulate template (Greicius et al., 2004) and an executive-control network based on a dorsolateral prefrontal template (Seeley et al., 2007). These two supplementary networks were used as controls to study the specificity of memory tasks to ATN basal connectivity.

Voxel wise and averaged basal functional connectivity of selected IC and group analysis

- *Voxel wise connectivity*

A double regression approach (Roosendaal et al., 2010b) was applied using the IC time course from each subject. Subsequent within and between group analyses (ANOVA $p<0.005$, corrected for cluster extent) was performed using the SPM5 software (Welcome Institute, London, UK) to achieve the positively correlated network with the given ICs.

Second level analysis (ANOVA) was performed to compare patients with controls. A mask was applied and only voxels within the positively correlated component were considered in the analysis.

In order to control for differences of gray matter volume between subjects, we calculated the mean value of gray matter volume within regions of interest that corresponded to the selected IC masks for each subject. We obtained, for each subject, a value of gray matter volume for the ATN, the default mode and the executive-control network. These values were entered as confounding covariates in both within and between group analyses. In order to minimize the partial volume effect of white matter, the statistical assessment was performed using an explicit gray matter mask.

- *Averaged connectivity within network*

A global connectivity index derived from the mean value of region of interest (Marsbar toolbox) corresponding to the significant clusters of the correlation maps was determined for each subject and each network. This index represents the value of the magnitude of the correlation between all the regions composing the network. It was compared between groups (patients vs controls) (Mann Whitney U) and sub-groups (mild ADs, aMCIs, memory complainers and control subjects) (Kruskal Wallis). It was also compared between each subgroup (Mann Whitney U).

Relationships between averaged basal connectivity of selected IC and neuropsychological data. The averaged connectivity values of the ATN and the two control networks were correlated with neuropsychological variables (Spearman's rank correlation coefficient; JMP software).

Results

Clinical, demographic and neuropsychological data

Group and subgroup effects on clinical, demographic and neuropsychological data were analyzed using Mann Whitney *U* test and Kruskal Wallis rank test for continuous variables and χ^2 test for dichotomous variables respectively.

Demographic and neuropsychological data of the twenty five subjects are reported in Table 1. No significant difference between patients and controls was observed concerning age ($p=0.89$, Mann Whitney *U* test), sex ($p=0.57$, χ^2 test) and educational level ($p=0.35$, Mann Whitney *U* test). As expected, patients performed significantly worse than controls on the MMSE and memory tasks. There was also a group effect on several executive tasks such as the digit-symbols coding subtest and Part B of the TMT. A subgroup effect on memory performance was also found, patients with mild AD obtaining the lowest scores and control subjects the highest scores (see Table 2).

Basal functional connectivity of the ATN

ATN extracted from ICA

The ATN extracted from ICA included the following medial and lateral temporal structures: the anterior superior, middle and inferior temporal gyrus (respectively Brodmann area (BA) 38, 20 and 21), the perirhinal (BA 35) and entorhinal cortices (BA 28; BA 34) and uncus (the hippocampal head and the ventral-medial portion of the amygdala). All values are significant at $p<0.005$, corrected for multiple comparisons at the cluster level (Fig. 1, Table 3).

Voxel wise basal functional connectivity alteration in the ATN

Voxel-based analysis of basal connectivity showed a significant increase of basal functional connectivity in patients relative to controls inside the inferior and superior temporal gyrus (BA 21; BA38) and in the left uncus ($p=0.046$; $k=10$; corrected for cluster

Table 1
Demographic and neuropsychological performances of patients and controls.

	Patients (N = 13) Mean (SD)	Controls (N = 12) Mean (SD)	p value[a]
Age	72 (9)	72 (7)	0.89
Sex (female/male)	4/9	5/7	0.57
Education (years)	13.6 (4.3)	12.2 (3.4)	0.35
MMSE	25.2 (2.45)	29.4 (1)	<0.0001
Memory tasks			
RL/RI 16 free delayed recall (16)	5.38 (4.94)	12.9 (2.23)	<0.0001
RL/RI 16 total delayed recall (free + cued) (16)	10.62 (5.52)	15.9 (0.32)	0.001
RL/RI 16 recognition (48)	44.25 (4.45)	48 (0)	0.002
DMS 48 Delayed recognition (100%)	84.46 (16.66)	99.8 (0.63)	0.002
Delayed recall of the Rey–Osterrieth figure (36)	8.25 (9.43)	28 (9.09)	0.002
Pyramid and Palm tree test (52)	49.67 (3.14)	52 (0)	0.011
Eve, total score (60)	25.85 (9.6)	49.44 (10.74)	0.001
Executive tasks			
WAIS-III matrix reasoning test (26)	12.33 (5.57)	16.25 (5.31)	0.094
WAIS-III digit span test (30)	14.08 (3.55)	14.78 (1.99)	0.586
WAIS-III digit-symbol coding test (133)	48.58 (17.02)	60.5 (11.15)	0.02
Trail making test part A (seconds)	52,15 (18,8)	34,83 (4,9)	0.054
Trail making test part B (seconds)	128 (40,02)	64,66 (27,77)	0.005
Visuo-perceptual task			
Benton face recognition test (27)	20.92 (2.63)	23 (2.24)	0.072

SD = Standard Deviation.
MMSE = Mini-Mental State Examination.
All performances correspond to raw score. Numbers in brackets in the first column refer to maximum scores.
WAIS = Weschler Adult Intelligence Scale.
DMS 48 = Delayed Matching to Sample-48 items-test.
RL/RI 16 = French version of the free and cued selective reminding test (FCSR).
[a] Group effects were analyzed using Mann–Whithney *U* test for continuous variables and χ^2 test for dichotomous variables.

extent) (Fig. 2 and Table 4). In contrast, no decrease in basal functional connectivity was observed in patients relative to controls.

Averaged basal functional connectivity alteration in the ATN

Averaged connectivity values of the ATN were significantly increased in patients relative to controls ($p = 0.008$; corrected for multiple comparisons; Mann Whitney *U* test). When comparing averaged connectivity inside the ATN across subgroups of subjects (mild ADs, aMCIs, memory complainers, controls), a significant effect was observed ($p = 0.01$; corrected for multiple comparisons; Kruskal Wallis test). Connectivity of the ATN was stronger in memory complainers and aMCI subjects than in mild AD patients (respectively $p = 0.043$ and $p = 0.05$; not surviving correction for multiple comparisons; Mann Whitney *U* test), and than in control subjects (respectively $p = 0.011$ and $p = 0.02$; not surviving correction for multiple comparisons; Mann Whitney *U* test). However, no difference was observed between aMCIs and memory complainers ($p = 0.221$; Mann Whitney *U* test). Mild AD patients and controls did not differ on averaged connectivity values of the ATN ($p = 0.467$; Mann Whitney *U* test). In sum, an effect was observed across subgroups ($p = 0.011$, corrected for multiple comparisons, Kruskal Wallis Test), memory complainers and aMCI subjects exhibiting strong ATN connectivity, while mild AD subjects displayed ATN connectivity comparable to normal controls (see Fig. 3).

Relationships between connectivity of the ATN and performance on neuropsychological tasks

Positive correlations were observed between averaged connectivity values of the ATN and memory performances in patients (see Table 5 and Fig. 4).

Firstly, positive correlations with performance were found on most tasks assessing anterograde memory: free delayed recall ($rho = 0.77$; $p = 0.002$; corrected for multiple comparisons), total delayed recall ($rho = 0.85$; $p = 0.0001$; corrected for multiple comparisons) and recognition of the RL/RI 16 ($rho = 0.92$; $p = 0.0001$; corrected for multiple comparisons), as well as with delayed recognition of the DMS 48 ($rho = 0.73$; $p = 0.004$; corrected for multiple comparisons). In contrast, no correlation was found with delayed recall score of the Rey–Osterrieth complex figure ($rho = 0.35$; $p = 0.26$).

Secondly, the analysis revealed a positive correlation between averaged connectivity values of the ATN and performance on tasks

Table 2
Memory performances obtained by the different subgroups of subjects: mild ADs, MCIs, memory complainers and controls.

Memory tasks	Mild ADs Mean (SD)	aMCIs Mean (SD)	Memory complainers Mean (SD)	Controls Mean (SD)	P value[a]
RL/RI 16 free delayed recall (16)	0.25 (0.5)	5.2 (3.42)	10.75 (9.5)	12.9 (2.23)	0.001
RL/RI 16 total delayed recall (free + cued) (16)	5 (2.83)	11.40 (5.55)	15.25 (0.95)	15.9 (0.32)	0.002
RL/RI 16 recognition (48)	41.75 (2.63)	44 (5.7)	48 (0)	48 (0)	0.001
DMS 48 Delayed recognition (100%)	71.75 (19.46)	82.6 (12.46)	99.5 (1)	99.8 (0.63)	<0.0001
Delayed recall of the Rey–Osterrieth figure (36)	4.75 (4.19)	4 (4.43)	20 (12.12)	28 (9.09)	0.008
Pyramid and Palm tree test (52)	47.75 (4.42)	49.8 (2.17)	52 (0)	52 (0)	0.008
Eve, total score (36)	23 (10.1)	23.8 (10.68)	31.25 (7.59)	49.44 (10.74)	0.007

All performances correspond to raw score. Numbers in brackets in the first column refer to maximum scores.
DMS 48 = Delayed Matching to Sample-48 items-test.
RL/RI 16 = French version of the free and cued selective reminding test (FCSR).
[a] Kruskal Wallis rank test.

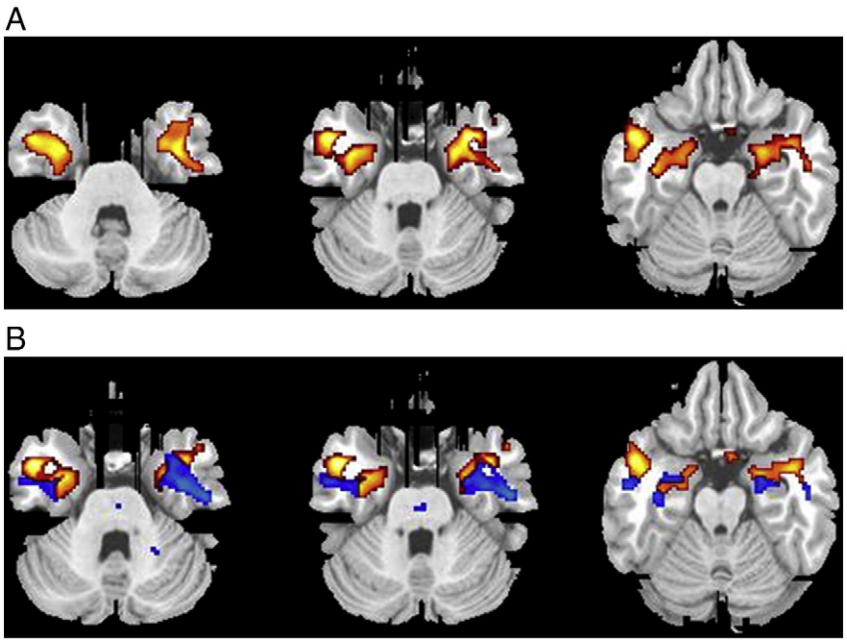

Fig. 1. Anterior temporal network obtained after double regression. Fig. 1A: Anterior temporal network determined by ICA and double regression ($p<0.005$, corrected for cluster extent) in the whole group of subjects. This network includes medial and lateral temporal structure: the anterior superior, middle and inferior temporal gyrus, the perirhinal and enthorinal cortices, the uncus (structure formed by the hippocampal head and the ventral-medial portion of the amygdala) (see Table 3). Fig. 1B: Anterior temporal network obtained in patients (hot) and controls (blue) showing a similar spatial pattern in both groups.

that assess retrograde semantic memory, such as the PPTT (rho = 0.66; $p=0.018$; not surviving correction for multiple comparisons). No significant correlation was found between connectivity values of anterior temporal network and performance on the EVE 10 (rho = 0.28; $p=0.33$). Finally, performance in executive and visuo-perceptual tasks did not significantly correlate with connectivity values of the ATN (see Table 5), with the exception of the part B of the TMT, for which a negative correlation was observed, which did however not survive correction for multiple comparisons (rho = −0.657; $p=0.02$). No significant correlation was observed in controls probably because of a lack of variability in performances.

Basal functional connectivity of the control networks and correlation with performance on neuropsychological tasks

Default mode network

The default mode network involved the posterior cingulate/precuneus (BA 7; BA 23; BA 30; BA 31), the inferior parietal lobule (BA 39; BA 40), the lateral temporal cortex (BA 22; BA 39), the premotor cortex (BA 8) and the parahippocampal cortex (BA 36). The hippocampal body and the superior frontal gyrus were not extracted at the defined threshold. Comparison of averaged connectivity value of the default mode network revealed no difference between groups ($p=0.277$) and subgroups ($p=0.289$) (see Supplementary Fig. 1 and Table 1).

Correlation analyses with neuropsychological performances revealed no significant correlation with memory or visuo-perceptual tasks in patients and controls. A positive correlation was however found with performance on the digit span in patients (rho = 0.605; $p=0.029$, not surviving correction for multiple comparisons).

Executive-control network

The executive-control network involved the anterior and dorso-lateral prefrontal cortex (BA 9; BA 10; BA 44; BA 45; BA 46), the orbito-frontal cortex (BA 47), the dorsomedial prefrontal cortex (BA 8), the anterior cingulate gyrus (BA 32), the premotor cortex and the supplementary motor area (BA 6) as well as the lateral parietal cortex (BA 39; BA 40) (see Supplementary Fig. 2 and Table 2). We found no

Table 3
ATN obtained after double regression analysis in the whole group of subjects.

Structures		Cluster k = 2133 p<0.001					
		Right hemisphere			Left hemisphere		
		Talairach coordinates			Talairach coordinates		
		x	y	z	x	y	z
Lateral temporal lobe	Superior temporal gyrus (BA 38)	35	13	−34	−49	2	−20
		49	12	−25			
	Middle temporal gyrus (BA 21)	45	−6	−14	−47	0	−25
	Inferior temporal gyrus (BA 20)				−37	−7	−26
Medial temporal lobe	Parahippocampal gyrus (BA 28; BA 34. BA 35)	25	−6	−23	−37	−16	−19
		19	−21	−12			
		13	5	−13			
	Uncus (the head of the hippocampus and ventral-medial portion of the amygdala)	35	1	−25	−19	−4	−19
					−33	−21	−10

Threshold $p<0.005$, corrected for multiple comparisons at the cluster level. Coordinates are provided in the Talairach space. BA: Brodmann area.

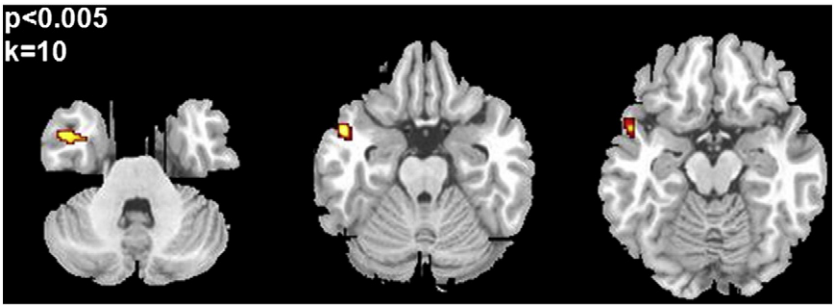

Fig. 2. Changes in functional connectivity observed in patients. Increased functional connectivity observed in patients inside the anterior temporal network. The second level group analysis comparing patients relative to controls (ANOVA, $p<0.005$; $k=10$; corrected for cluster extent) showed a significant increased basal functional connectivity inside the anterior segment of the left inferior and superior temporal gyrus and the left uncus (see Table 4).

significant difference of the averaged connectivity value of this network between patients and controls, or between subgroups. Correlation analyses with neuropsychological performances revealed no significant correlation with memory or visuo-perceptual tasks. Significant negative correlations were however observed with both part A ($rho=-0.808$; $p=0.001$, corrected for multiple comparisons) and part B ($rho=-0.713$; $p=0.009$, corrected for multiple comparisons) of the TMT.

Discussion

Using resting-state fMRI, specific changes of basal functional connectivity within an ATN were found in a population with heterogeneous performance on tasks assessing memory, characterized by increased connectivity of the ATN in subjects with impaired memory. In addition, performance on declarative memory tasks was associated with the magnitude of basal functional connectivity of this ATN. These correlations appeared to be specific to declarative memory, as no correlation was observed with other evaluated cognitive measures. Furthermore, the correlations with performance on memory tasks appeared to be specifically related to the ATN, as no correlation was found with two other networks that were selected for comparison.

The ATN reported here is likely to reflect a functional-anatomic network, although many methodological challenges have to be considered when assessing basal functional connectivity using resting-state fMRI. In the present study, sources of physiological artifacts were reduced using regression of non neuronal signal on functional images, in particular the signal correlation related to physiological noise (CSF, cardiac pulsation, large arteries and veins pulsations, breathing and motions). Moreover, altered functional connectivity reported here was found to be network specific (changes concerned only the ATN) and associated with specific cognitive tasks (correlations with memory tasks for the ATN and with tasks assessing attention for the executive-control network).

Change in basal functional connectivity of the ATN in patients with impaired memory

In the present study, increased connectivity of the selected ATN was observed in subjects with impaired memory, relative to controls. This increase was found using both a voxel-wise analysis and a global analysis based on averaged connectivity values. These two measures provide complementary information, the former measuring the spatial localization of connectivity changes within the network, and the latter the magnitude of this connectivity.

These results may reflect functional changes associated with clinically relevant dysfunction at the neural system level. Altered functional basal connectivity has been reported in various neurological or psychiatric conditions such as epilepsy (Addis et al., 2007; Bettus et al., 2009; Waites et al., 2006), brain tumors (Bartolomei et al., 2006; Bosma et al., 2008), schizophrenia (Bluhm et al., 2007; Fakra et al., 2008; Jafri et al., 2008; Whitfield-Gabrieli et al., 2009; Zhou et al., 2008) and multiple sclerosis (Lowe et al., 2002; Rocca et al., 2010; Roosendaal et al., 2010a). Functional basal connectivity has also been investigated in detail in AD (Bokde et al., 2009; Liu et al., 2008; Sorg et al., 2009, for review). Several groups have reported decreased intrinsic connectivity between the posterior default mode network and medial temporal lobe structures not only in AD but also in patients with MCI, a transitional stage between normal aging and dementia (Allen et al., 2007; Bai et al., 2008; Greicius et al., 2004; He et al., 2007; Li et al., 2002; Qi et al., 2010; Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2006; Zhou et al., 2010).

Paradoxically and consistent with our findings, dysfunction in functional basal connectivity may also lead to hyperconnectivity of networks, especially in the earliest stages of progressive diseases. Task-related functional MRI studies have demonstrated hyperactivation within MTL structures in MCI subjects (Dickerson et al., 2004; Hamalainen et al., 2007; Miller et al., 2008; Sperling et al., 2010 for review). For example, Dickerson et al. (2004) demonstrated that, in a

Table 4
Local functional hyperconnectivity observed in patients inside the ATN.

Region	BA	Talairach coordinates			Cluster size	p value
		x	y	z		
Left middle temporal gyrus	21	−49	4	−20	228	0.04
Left superior temporal gyrus	38	−47	11	−8		
Left uncus		−31	−1	−28		

Threshold $p<0.005$, corrected for multiple comparisons at the cluster level.

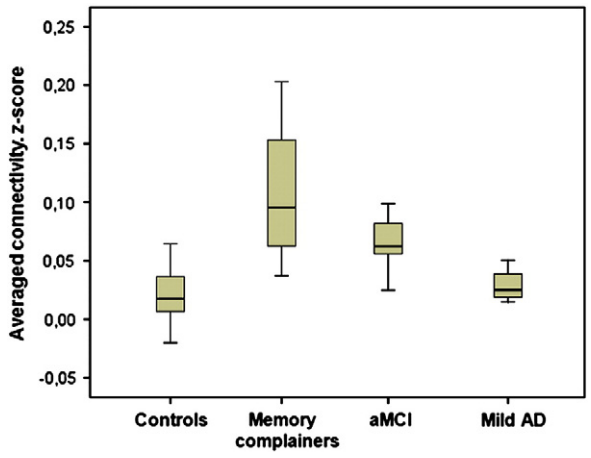

Fig. 3. Averaged connectivity values (Z-scores) of the anterior temporal network in subgroups of subjects: mild ADs, aMCIs, memory complainers, controls. A significant subgroup effect was observed ($p=0.011$, Kruskal Wallis test). Memory complainers and MCI subjects exhibited strong connectivity values of ATN, while mild AD subjects displayed ATN connectivity values comparables to controls.

Table 5
Correlations between global connectivity values of ATN and cognitive performances in the whole group of patients.

	Spearman rho	p
RL/RI 16 free delayed recall	0.77	0.002
RL/RI 16 total delayed recall	0.85	<0.0001
RL/RI 16 recognition	0.92	<0.0001
DMS 48 delayed recognition	0.73	0.004
Delayed recall of the Rey–Osterrieth figure	0.35	0.263
Pyramid and Palm tree test	0.66	0.018
EVE, total score	0.28	0.338
WAIS-III matrix reasoning test	0.37	0.226
WAIS-III digit span test	0.15	0.617
WAIS-III digit symbol coding test	0.24	0.441
Trail Making test part A	−0.35	0.239
Trail Making test part B	−0.657	0.02
Benton face recognition test	0.15	0.625

DMS 48 = Delayed Matching to Sample-48 items-test.
RL/RI 16 = French version of the free and cued selective reminding test (FCSR).
WAIS = Weschler Adult Intelligence Scale.

picture-encoding task, MCI subjects displayed greater parahippocampal gyrus activation relative to controls. Interestingly, greater MTL activation was associated with better memory performance. Finally, subjects who declined after longitudinal follow-up activated to a greater extent the right parahippocampal gyrus at baseline compared with those who remained stable. The findings of the present study are partially in line with those reported by Celone et al. (2006) who found a non linear pattern of functional connectivity during an associative memory task in a population representing a continuum from normal aging to mild AD. They observed that very mildly impaired MCI patients demonstrated evidence of paradoxically increased activation in the hippocampus and functionally connected neocortical regions. However, unlike the present study, an increased deactivation in the default network compared with controls was reported and patients with MCI that were more impaired showed significantly decreased hippocampal activation and reduced deactivation in default regions, in a pattern similar to patients diagnosed with mild AD. Whether the discrepancy of these findings with those reported in the present study could be related to differences concerning the neuropsychological profile of the selected population or to differences in the experimental setting (resting versus

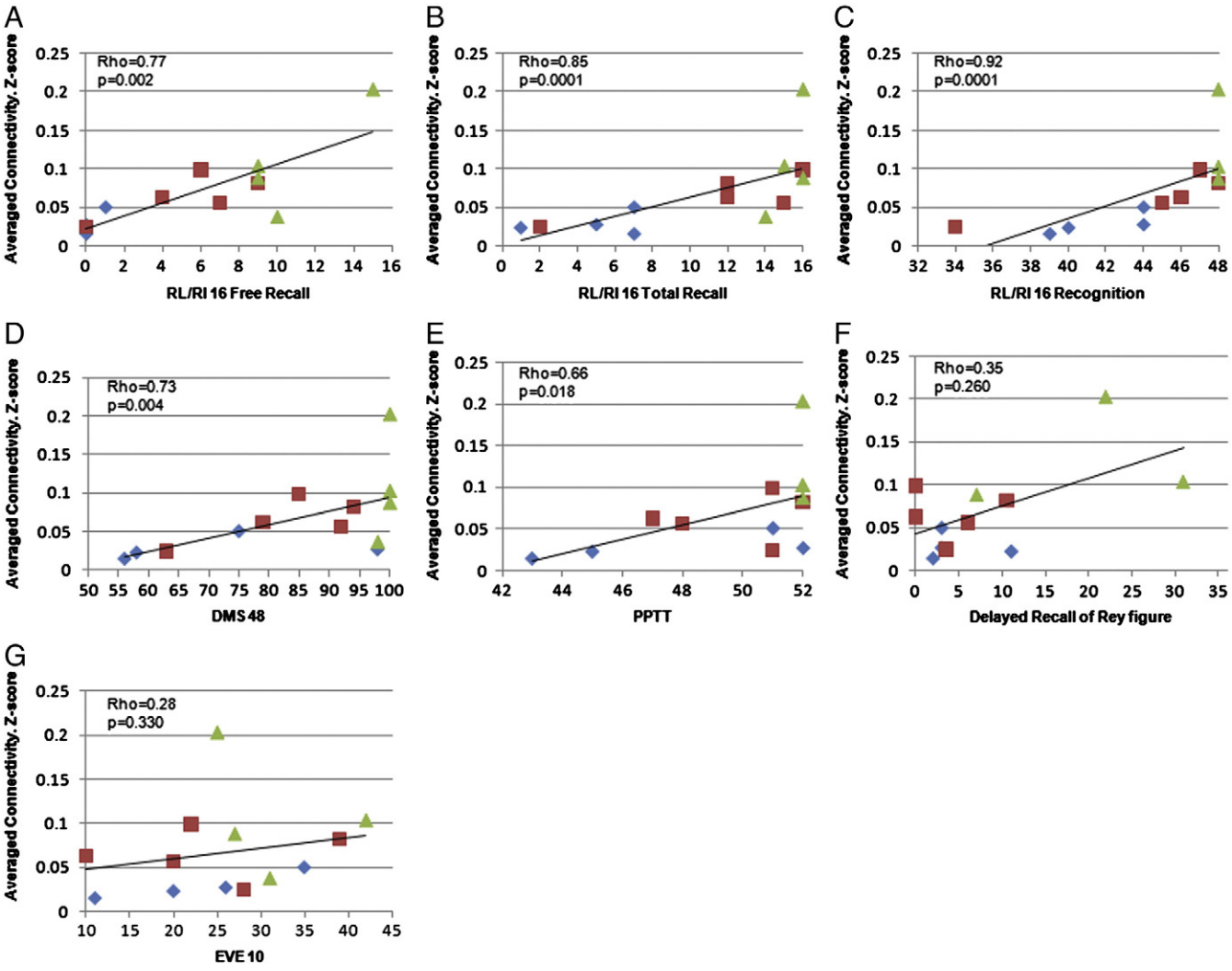

Fig. 4. Correlations between averaged basal functional connectivity of ATN and memory performances in patients. Red squares: aMCIs; Blue diamond: mild ADs; Green triangle: Memory complainers. Positive correlations with performances were found on Free delayed recall (rho = 0.77; p = 0.002; corrected threshold) (Fig. A), total delayed recall (rho = 0.85; p = 0.0001; corrected threshold) (Fig. B) and recognition (rho = 0.92; p = 0.0001; corrected threshold) (Fig. C) of the RL/RI 16, recognition of the DMS 48 (rho = 0.73; p = 0.004; uncorrected threshold) (Fig. D) and PPTT performance (rho = 0.66; p = 0.018; uncorrected threshold) (Fig. E). In contrast, no significant correlation was found between connectivity values of anterior temporal network and performances on the delayed recall of the Rey figure (Fig. F) and EVE 10 score (Fig. G) (see also Table 5).

task-related state) remains to be determined. In resting-state fMRI studies, increased connectivity has been observed in patients with MCI and mild AD (Qi et al., 2010; Wang et al., 2006; Wang et al., 2007). Qi et al. (2010) investigated basal functional connectivity of the default mode network and found both hypoconnectivity and hyperconnectivity in MCI relative to controls. Wang et al. (2006) have evaluated the functional connectivity of the hippocampi in mild AD and controls. They found decreased connectivity between the right hippocampus and key regions of the default mode network, but increased connectivity between the left hippocampus and the right lateral prefrontal cortex. This hyperconnectivity/hyperactivation phenomenon is commonly explained in terms of compensatory processes to cope with cognitive deficits in the setting of early pathology.

Here, consistent with this hypothesis, we evidenced in the patient group increased connectivity of the ATN and positive correlations with performance on tasks assessing memory. Stronger values of connectivity of the ATN were associated with better performance on memory tasks, suggesting that hypersynchronization may reflect compensatory processes in the setting of early memory network dysfunction at the neural system level. Specifically, in the present study, changes in basal functional connectivity of the ATN were observed in subjects with isolated memory complaint and aMCI patients, which represent two populations at risk for AD (Dawe et al., 1992; Geerlings et al., 1999). This could indicate that basal functional connectivity increases during the preclinical or earliest clinical stages of neurodegenerative diseases, within neural systems carrying minimal pathological burden. A progressive decrease of connectivity strength may subsequently occur, paralleling disease progression. In this framework, similar ATN connectivity in early AD patients and controls could be explained by the trajectory of the connectivity strength, while crossing the normal level. It is possible that, as the stage of disease advances, subjects would then demonstrate decreased functional connectivity of the ATN, as previously demonstrated by Greicius et al. (2004) and Zhou et al. (2010), among others within the default mode network.

That there was no difference of connectivity strength of the default mode and executive-control networks between the patient subgroups and controls is consistent with the neuropsychological profile of the patients' group. Yet, they potentially present a preclinical or early clinical stage AD in which these two networks are not expected to be functionally altered. This is also in line with the progression of neuropathological change in AD, since neurofibrillary tangles related to Tau protein pathology, and associated with clinical signs (Arriagada et al., 1992; Bennett et al., 2005; Gomez-Isla et al., 1997), initially develop in medial temporal structures within the ATN (Braak and Braak, 1991; Delacourte et al., 1999), outside the two selected control networks.

The ATN seems to be the site of early changes in memory dysfunction. Previous works, focusing on other basal networks, suggested that resting-state fMRI may serve as a functional bioimaging marker and may improve the diagnosis of diseases such as AD (Greicius et al., 2004; Koch et al., 2010; Wang et al., 2006; Zhou et al., 2010). To what extent the basal connectivity changes of the ATN found here may be an interesting tool to predict early AD pathology would require further studies with a greater number of subjects, and available follow-up and/or biomarker data.

Relationship between basal functional connectivity of the ATN and declarative memory performance

In this study, there was a strong correlation between the magnitude of basal functional connectivity of the selected ATN and performance on several anterograde and retrograde declarative memory tasks. By contrast, no correlation was observed with other evaluated cognitive domains such as executive and visuo-perceptual functions, suggesting a task-specific effect. In addition, there was no correlation between either the default mode or the executive-control network with performance on memory tasks, further suggesting that the connectivity within the ATN is specifically related to declarative memory.

As expected, we found significant negative correlations between the connectivity of the executive-control networks and parts A and B of the TMT. In other words, the magnitude of connectivity of this executive-control network was positively correlated with performance, expressed here in terms of time to complete the task. The Trail making test is commonly used as a measure of frontal executive function, part A being associated with sustained visual attention and psychomotor speed, and part B with additional cognitive flexibility associated with divided attention (Arbuthnott and Frank, 2000). However, this task is also influenced by other variables, such as for instance, alphabet manipulation, which also requires semantic processing, as reflected by the correlation observed between part B of the Trail Making Test and ATN. Yet, and consistent with this hypothesis Zakzanis et al. (2005) using fMRI observed, when comparing part B with part A, dorso-lateral and medial frontal activations but also middle and superior temporal lobe activation.

In the same line, we also observed a trend for a positive correlation between performance at digit span and the default mode network. The digit span task is also a widely used measure of verbal sustained attention and working memory. It requires the short-term mental manipulation of numbers, and is associated with activity in the left dorsolateral prefrontal cortex, but also with parts of the default mode network such as inferior parietal lobe structures (Forn et al., 2009).

Thus, basal connectivity at rest may provide clues on the efficiency of a given network during specific tasks. Coherent spontaneous fluctuations in brain systems may have functional implications and be relevant to individual variability in human behavior. This has recently been illustrated in studies on healthy subjects focusing on prefrontal and somatomotor networks. For example, spontaneous fluctuations within the human somatomotor system were found to predict trial to trial variability in the force of a button press (Fox et al., 2007). Hampson et al. (2006) demonstrated that performance on a working memory task was positively correlated with the strength of functional connectivity between the posterior cingulate cortex and medial prefrontal/ventral anterior cingulate cortices at rest. Prescan anxiety rating has been found to correlate with spontaneous connectivity within the frontoinsular anterior cingulate “salience” network, whereas set-shifting performance has been associated with fronto-parietal executive control network (Seeley et al., 2007).

In the field of declarative memory, basal functional connectivity is only beginning to be investigated. We specifically selected the ATN because of the well-known implication of its components in memory processes, but also in the earliest stages of Alzheimer's disease. At rest, this network was first delineated by Kahn et al. (2008) in healthy controls, using a region-of-interest based method. Here, using a data-driven approach based on ICA, we extracted a similar ATN pattern. We also found that averaged basal connectivity values inside the ATN were associated with performance on several tasks assessing declarative memory. In particular, strong positive correlations were observed with performance on anterograde memory tasks assessing delayed recall and recognition of single-items such as concrete words (the RL/RI 16) and pictures of objects (the DMS 48). In contrast, no correlation was found with the delayed recall of complex material (such as the Rey–Osterrieth figure). Regarding retrograde memory, the correlation analysis also revealed positive correlations between functional connectivity of the ATN and performance on a semantic object-based memory task, such as the PPTT.

These results can be interpreted within the context of models of declarative memory. One classical view of memory organization considers declarative memory as a unitary system relying on medial temporal lobe (MTL) region (Squire et al., 2007). Alternatively,

declarative memory could depend on a series of distinct, relatively independent, anatomo-functional systems: an anterior subhippocampal system involving context-free memory (e.g., familiarity-based recognition and semantic memory) and a hippocampal system involving context-rich memory (episodic memory and spatial memory). Several lines of evidence favor this alternative view, partly derived from functional dissociations observed in experiments in non-human primates (Meunier et al., 1993) and humans (e.g., Barbeau et al., 2006; Barbeau et al., 2005; Mayes et al., 2004; Tramoni et al., 2009; Tramoni et al., 2011; Vargha-Khadem et al., 1997). These studies suggest that anterior subhippocampal structures are involved in semantic memory, memory for objects and memory for single items (i.e. stimuli that are processed at the exemplar level independently of any context). By contrast, the hippocampal formation is thought to play a crucial role in the association of relationships among items, elements and places that characterizes episodic and spatial memory, to be further distributed in neocortical regions. This view has been conceptualized in a hierarchical model of declarative memory (Mishkin et al., 1997; Mishkin et al., 1998). Accordingly, anterior subhippocampal cortices receive inputs from cortical sensory areas, in particular from the visual ventral stream and convey information to the hippocampus situated at the top of the hierarchy. Beyond their respective differences, other groups have elaborated similar models (Aggleton and Brown, 1999; Eichenbaum et al., 2007).

Interestingly, the modular model proposal is in fact also supported by basal functional connectivity studies. As previously mentioned, using resting-state fMRI, two separate brain networks within the MTL were delineated by Kahn et al. (2008), an ATN which was the focus of the present study, and a posterior network which included the body of the hippocampus, the posterior parahippocampal cortex, the lateral parietal cortex, along with posterior midline structures and ventral medial prefrontal cortex. Wang et al. (2010b) found that the strength of functional connectivity between bilateral hippocampi measured during rest predicted individual performances in the recall of previously encoded memory material. In another study, they demonstrated that individual differences in performance on associative episodic memory and story recall tasks could be predicted by individual differences in intrinsic hippocampal-posteromedial cortical connectivity during resting state (Wang et al., 2010a). Conversely, we showed in the present study that the basal functional connectivity of the ATN was strongly correlated with both anterograde single-items and retrograde object-based semantic memory performance, supporting the view that this network could be involved in acquisition and maintenance of some form of object-based semantic knowledge. In addition, we found no correlation with the delayed recall of a complex material such as the as the Rey–Osterrieth figure. This task, which requires the recollection of complex spatial relationships among different elements (that compose the figure), probably requires the implication of the posterior hippocampus and related structures (i.e., the posterior temporal network), as also suggested by brain-damaged-studies (Barbeau et al., 2006; Barbeau et al., 2010; Vargha-Khadem et al., 1997). In the same line, there was no correlation between basal functional connectivity of the ATN and a task assessing knowledge of remote public events, which may also requires the reactivation of some forms of episodic memory traces. Indeed, public events are inserted within a specific spatiotemporal context such as, for example, mental state and emotions associated with the event (Cermak, 1984; Thomas-Anterion and Puel, 2006). In support of this hypothesis, Thomas-Anterion et al. (2001) described a case of memory impairment after meningoencephalitis with a dissociation between preserved semantic autobiographical memories and impaired episodic autobiographical memories associated with impaired public events knowledge. Taken together, these results provide additional evidence that the basal level of posterior and anterior temporal networks are associated with distinct memory components, and therefore support a modular view of declarative memory organization within medial temporal lobe structures.

Conclusion

The present study, using resting-state fMRI, focused on an ATN, the components of which have been shown to be critical for declarative memory and the site of the earliest changes in Alzheimer's disease (AD). The results provide new insights into the relationships between basal functional connectivity and behavioral performance. ATN was hyperconnected in patients with impaired memory and averaged connectivity values of ATN at rest were specifically and positively correlated with anterograde and retrograde object-based memory performance. These findings suggest that increased connectivity at rest reflects the involvement of compensatory processes that precociously take place in the face of pathology. These results may also be relevant for our understanding of the neural underpinning of declarative memory, highlighting the functional role of basal ATN in object, context-free-based memory.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2011.05.090.

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Supplementary tables

Table 1. The default mode network

Region	BA	Talairach coordinates			Cluster size	P (p<0.005, corrected at the cluster level)
		x	y	z	k	
Right and Left posterior cingulum cortex	23-30-31	5 1 -7	-43 -41 -53	24 33 13	1073	<0.0001
Right and left precuneus		9 -1	-48 -50	34 37		
Right parahippocampal gyrus	36	23	-41	-8		
Right inferior parietal lobule Right temporal superior gyrus	39 40 22-39	41 51 51	-54 -51 -55	37 26 19	740	<0.0001
Left inferior parietal lobule Left temporal superior gyrus	39	-41 -49	-50 -57	33 24	507	<0.0001
Left superior frontal gyrus	8	-24	38	48	408	<0.0001

Threshold $p < 0.005$, corrected for multiple comparisons at the cluster level. Coordinates are provided in the Talairach space. BA: Brodmann area.

Table 2. The executive-control network

Region	BA	Talairach coordinates			Cluster size	P (p<0.005, corrected at the cluster level)
		x	y	z	k	
Right medial frontal gyrus	8	35	15	34	2908	<0.0001
Right middle frontal gyrus	9	33	17	37		
Right inferior frontal gyrus	44-45-46-47	39 41 29 37	9 28 19 35	29 18 -2 20		
Right superior frontal gyrus	6	7	14	54	2535	<0.0001
Left and right superior medial frontal gyrus	8-10	-1 9	35 46	42 1		
Right cingulate gyrus	32	3	35	27		
Left middle frontal gyrus	10	-33	45	12	218	0.012
Left middle frontal gyrus	8-9	-35 -37	13 17	43 35	624	<0.0001
Left inferior frontal gyrus	45-46	-39	26	22		
Left superior frontal gyrus	8	-19	23	44		
Right inferior parietal lobule	39-40	45 37	-40 -56	40 37	275	0.013

Threshold $p < 0.005$, corrected for multiple comparisons at the cluster level. Coordinates are provided in the Talairach space. BA: Brodmann area.