Network Interactions Explain Effective Encoding in the Context of Medial Temporal Damage in MCI

Andrea B. Protzner,^{1,2} Jennifer L. Mandzia,³ Sandra E. Black,^{3,4}
and Mary Pat McAndrews^{1,2*}

¹Krembil Neuroscience Centre, University Health Network, Toronto, Ontario, Canada

²Department of Psychology, University of Toronto, Toronto, Ontario, Canada

³L.C. Campbell Cognitive Neurology Research Unit, Neurosciences Research, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

⁴Department of Medicine, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

Abstract: Selective dysfunction in the medial temporal lobe (MTL) in amnesic mild cognitive impairment (MCI) results in a relatively circumscribed impairment in episodic memory. Previously, we found that activation extent in MTL during encoding correlated with subsequent recognition (hit rate) in controls but not in MCI patients (Mandzia et al. [2009]: *Neurobiol Aging* 30:717–730). Here, we examined whether functional connectivity amongst MTL and cortical regions might better explain differences in subsequent recognition success. Participants underwent fMRI scanning during picture encoding, and multivariate analysis was used to characterize the relationship between network activations and recognition. Both patients and controls activated a canonical MTL encoding network. However, this network correlated with hit rate only for controls. In MCI patients, recognition variability was best explained by the engagement of an additional network including BA 20. We propose that this pattern represents functional reorganization caused by reduced efficiency in the MTL network. Our findings suggest that understanding brain-behavior relationships in neurological disorders requires examination of large-scale networks, even when dysfunction is relatively focal as in MCI. *Hum Brain Mapp* 32:1277–1289, 2011. © 2010 Wiley-Liss, Inc.

Key words: fMRI; amnesic mild cognitive impairment; medial temporal lobe; memory encoding; recognition performance

INTRODUCTION

Our ability to make predictions about clinical outcome following regional brain damage remains imperfect. For example, both lesion and functional neuroimaging research suggests that the medial temporal lobe (MTL) is critical for episodic memory formation and retrieval [Eichenbaum, 2006; Milner et al., 1968; Squire, 1992]. However, researchers have found it challenging to relate the degree of MTL activation to the degree of clinically relevant memory impairment associated with focal disturbance in this region. Although there has been some success in showing a clear relationship in cases of unilateral temporal lobe epilepsy [Richardson et al., 2004, 2006], the situation with

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*Correspondence to: Mary Pat McAndrews, Krembil Neuroscience Centre, University Health Network, 399 Bathurst Street, Rm. 4F-409, Toronto, ON, M5T 2S8. E-mail: mcandrows@uhnres.utoronto.ca

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progressive disorders such as amnesic mild cognitive impairment (MCI)¹ and Alzheimer's disease (AD) is considerably more complicated. Several functional neuroimaging studies have examined task-induced activation patterns in MCI patients relative to controls, and revealed increases [Celone et al., 2006; Dickerson et al., 2004, 2005], decreases [Johnson et al., 2004; Machulda et al., 2003], as well as spatial differences in activation [Celone et al., 2006]. Recent work by Sperling and colleagues [Celone et al., 2006; Dickerson and Sperling, 2008] suggests that the function relating clinical memory impairment to magnitude of activation is nonmonotonic. Patients with very mild MCI show MTL *hyperactivation* relative to controls during memory encoding whereas those with more severe memory impairments show *hypoactivation*. This complex pattern indicates that assessment of the functional consequences of focal damage based on activation data likely requires a more comprehensive view of patterns of engagement and interaction across brain regions.

We hypothesized that an alternate strategy to predicting clinically relevant memory impairment in progressive disorders is to consider how MTL damage affects encoding networks. Some studies have begun to investigate this relationship in affected populations [Bai et al., 2009; Celone et al., 2006; Wagner et al., 2007]. In MCI, Bai et al. [2009] reported that functional connectivity with the hippocampus during a memory retrieval task was more diffuse in patients than controls. Furthermore, the strength of "atypical" connections was negatively correlated with neuropsychological test (mental status, verbal memory, attention, and psychomotor speed) performance. Celone et al. [2006] used independent component analysis to identify brain regions with temporally synchronous activity during a face-name associative memory paradigm. They found that bilateral inferior frontal regions showed a similar pattern to the hippocampus, in that milder MCI patients showed hyperactivation relative to controls whereas more impaired MCI and AD patients demonstrated hypoactivation in these regions. Only hippocampal activation was correlated with task performance as measured by hit rate; other regions involved in the encoding network did not demonstrate such a correlation. Importantly, these analyses were not aimed at identifying the networks that facilitate subsequent recall in patients with MTL damage, or how alternative (i.e., compensatory) networks emerge when canonical networks are disabled.

In a previous study, we used fMRI to measure brain activation patterns associated with incidental encoding of photographs in MCI patients and controls [Mandzia et al., 2009]. We found equivalent medial temporal activation in controls and MCI patients; while the degree of

TABLE I. Group demographics and neuropsychological performance

	MCI Patients, N = 14 (7 F/7 M)	Healthy controls, N = 14 (7 F/7 M)
Mean age, range	68.6 ± 7.4 (59–81)	72.2 ± 6.4 (63–81)
Years of education, range	13.4 ± 2.8 (10–18)	15.4 ± 2.8 (11–19)
MMSE	27.7 ± 1.1	28.6 ± 1.1
CDR	0.5	—
CDR, sum of boxes	1.5 ± 0.99	—
Mattis Dementia Rating Scale	135.1 ± 4.3	140.9 ± 2.1
CVLT, acquisition ^a	31.6 ± 11.2	50 ± 6
Boston naming ^a	25.7 ± 2.2	28.7 ± 1.4
Backward digit span	7.9 ± 3.3	7.8 ± 1.9
Wisconsin card sort categories	2.8 ± 1.3	3.4 ± 1.3

MMSE, mini-mental status examination; CDR, Clinical Dementia Rating Scale; CVLT, California Verbal Learning Test. A CDR for normal controls was not done.

^aSignificant group differences $P < 0.05$ from GLM neuropsychological testing.

activation correlated with recognition success as measured by hit rate in controls, it did not explain performance variation in patients. Here, we used a multivariate analysis technique, partial least squares (PLS), to examine group differences in MTL functional connectivity in relation to subsequent memory performance. This allowed us to explore whether compensatory patterns might emerge in a performance-driven (rather than task-driven) analysis.

METHODS

Participants

The experimental design has been described in detail in another article [Mandzia et al., 2009]. Briefly, 17 MCI patients and 16 normal controls took part in the experiment. Data from three MCI patients and two normal controls were excluded due to problems with motion in the scanner. The remaining sample consisted of 14 MCI patients (seven females) and 14 normal controls (seven females). Amnesic MCI patients were recruited from the Sunnybrook Cognitive Neurology Clinic. They were categorized as MCI patients based on a structured interview, neuropsychological testing and clinical examination. Relevant demographic and clinical data are shown in Table I. MCI patients exhibited subjective memory complaints verified by an informant, with performance greater than or equal to 1 standard deviation below age and education adjusted norms on memory tests (acquisition or delayed recall of the California Verbal Learning Test [Delis, 1987] or on long delay of logical memory from the Wechsler Memory Scale [Wechsler, 1987]), MMSE score ≥ 24 and an overall Clinical Dementia Rating (CDR) = 0.5 [Morris, 1993]. Note that 10 patients met the Petersen criteria for MCI: lack of global cognitive or

¹Although aMCI can be considered a prodromal state to Alzheimer's disease, not all patients eventually convert and we cannot verify that status for the current sample.

functional impairment (MMSE and CDR scores) with mild (1.5 SD) memory impairment. The remaining four patients had slightly milder memory impairment (between 1 and 1.5 SD), but otherwise met the Petersen criteria. Secondary causes of MCI such as vascular, metabolic, nutritional, or mood disorders all were excluded through the standardized work-up. Of note, our MCI patients were somewhat more impaired than those included in the mild group in the study of Celone et al. [2006].²

Controls were healthy community volunteers. All underwent comprehensive neuropsychological testing as well as structural MRI to ensure they were normal for their age and had no concomitant neurological or psychiatric disorders, and were not taking any psychotropic or cognitive enhancing medications. It was not feasible to perform the CDR on the normal control group, but a preassessment telephone screening suggested that they had no cognitive complaints or functional limitations. Relevant demographic and clinical data are shown in Table I. All participants gave informed consent in accordance with the Sunnybrook Research Ethics board.

fMRI Task

The current article uses only a part of the data collected for the original study and here we describe only those aspects of data collection pertinent to the current study [Mandzia et al., 2009]. During the incidental deep encoding task, participants viewed photographs (half color and half black and white) of objects and animals, and pressed a response button to indicate whether each photograph depicted a “natural” or a “man-made” object. During the baseline task, participants viewed one scrambled photograph repeatedly, and pressed both response buttons when the stimulus appeared.

Encoding data were collected in one imaging run, which consisted of six encoding blocks (31 s) interleaved with five baseline blocks (26 s). There were five stimuli (photographs or the scrambled pattern) per block with a text instruction (6 s) at the beginning of each block. In the encoding blocks, each photograph was presented for 4 s with an interstimulus interval (ISI) of 1 s. In the baseline blocks, the scrambled pattern was presented for 3 s with an ISI of 1 s. Following encoding, three-dimensional T1-weighted anatomical scanning (see below) was performed to create a 12 min delay between encoding and recognition tasks. During a subsequent scan (fMRI data not presented here), participants made yes/no recognition decisions on 15 pictures presented during encoding blocks intermixed with 15 new pictures. In the current study, we use hit rate from this recognition task as our behavior measure.

²Celone et al. (2006) used CDR sum-of-boxes scores to subdivide their mild and more impaired MCI patients. Their mild MCI patients scored 1.1 ± 0.4 , and more impaired patients scored 2.5 ± 0.6 . The MCI patient in the current study scored 1.5 ± 0.99 .

For most participants, stimuli were presented using MRI-compatible goggles (Silent Vision, Avotec, Jensen Beach, FL) that allowed for adjustments for visual acuity. The first five normal control participants viewed the stimuli projected onto a screen at the foot of the MRI patient table. Accuracy and reaction time were recorded using an MRI-compatible keypad (Lumitouch, Lightwave Technologies, Surrey, BC). Participants indicated their response choice by pressing the right button (for natural and old photographs) or the left button (for man-made and new photographs) with the middle or index finger of their right hand, respectively. During the fixation condition, they pressed both buttons when the scrambled color pattern appeared. Stimuli were counterbalanced for color and type of photograph (natural vs. man-made).

fMRI Imaging Protocol

The study was conducted on a whole-body MRI system operating at 1.5 Tesla magnetic field strength (Signa, GE Medical Systems, Waukesha, WI; CV/I hardware, LX8.4 software). Single shot spiral imaging was performed with imaging parameters to optimize BOLD contrast [Ogawa et al., 1990] and included offline gridding, reconstruction, and correction for magnetic field inhomogeneity and Maxwell gradient terms (TR = 3 s, TE = 40 ms, 64×64 matrix, 30–34 slices, $3.1 \times 3.1 \times 5$ mm³) [Glover and Lai, 1998]. Coronal scans were performed to maximize signal intensity and minimize partial volume effects in the MTL. Three-dimensional anatomical MRI scanning was performed with higher spatial resolution (fast spoiled gradient echo imaging, field of view = 22 by 18 cm, flip angle/TE/TR/ = 35 degrees/6 ms/15 ms, 256×192 , 128 axial slices 1.5-mm thick).

fMRI Analysis

Using Analysis of Functional NeuroImaging (AFNI) software [http://afni.nimh.nih.gov/, Cox, 1996], time series data were spatially coregistered to correct for head motion by using a 3D Fourier transform interpolation. After motion correction, additional artifacts were removed using probabilistic independent component analysis (ICA) with MELODIC [Multivariate Exploratory Linear Optimized Decomposition into Independent Components; Beckmann and Smith, 2004]. Probabilistic ICA assumes that artifacts present in fMRI data follow a non-Gaussian distribution. It is a blind source separation technique that decomposes a two-dimensional data matrix (time $\times$ voxels) into a set of time courses with associated spatial maps, which jointly describe the temporal and spatial characteristics of statistically independent latent variables (source signals). Artifacts were identified and removed following the guidelines outlined by Beckmann and Smith [2004, 2005]. After ICA denoising, images were registered to the MNI EPI template as implemented in SPM5 [http://www.fil.ion.ucl.ac.uk/spm/, Friston et al., 1995]. The transformation of each participant

to the EPI template was achieved using a 12-parameter affine transform with sinc interpolation. Images were smoothed with an 8-mm isotropic Gaussian filter before analysis. For each participant, “brain” voxels in a specific image were defined as voxels with intensities greater than 15% of the maximum value in that image. The union of masks was used for group analyses as described below.

Data Analysis

The primary image analysis was done with PLS. Task PLS is a multivariate technique that enables the identification of the optimal spatial patterns that differentiate tasks and groups in terms of activation. Behavior/seed PLS is a multivariate technique that enables the identification of the optimal spatial patterns that differentiate tasks and groups in terms of functional connectivity and brain-behavior correlations [for a detailed description of PLS’s application to blocked design fMRI data, see McIntosh et al., 1996]. PLS operates on the entire data structure at once (i.e., all groups and conditions), which requires that the data be in matrix form. The rows of the data matrix are arranged as follows. Subject groups are stacked. Within group, condition blocks are stacked and each participant has a row of data within each condition block. With g groups, n participants and k conditions, there are $g \times n \times k$ rows in the matrix. The columns of the data matrix contain the signal intensity for each voxel. This is expressed as the block average signal intensity for each voxel minus the intensity for that voxel at block onset. The first column has intensity for the first voxel, the second column has the intensity for the second voxel. With m voxels and t time points, there are $m \times t$ columns in the matrix.

Three forms of PLS were performed. The first, task PLS, assessed whether there were differences between groups in task-dependent brain activity. This analysis allowed us also to identify a region of interest (ROI; i.e., seed voxel) in the MTL whose activity reliably differentiated encoding from baseline tasks. The second, behavior PLS, was performed only on MCI data to identify the voxel whose activity changes most reliably correlated with changes in hit rate (i.e., had the highest bootstrap ratio). The third, seed/behavior PLS assessed whether there were group-dependent changes in cortical regions that were functionally connected with the seed voxel during encoding, and also facilitated subsequent recognition (i.e., brain-seed-behavior correlation).

Task PLS

Task PLS uses singular value decomposition to identify distributed activity patterns, or latent variables (LV), that show similarities or differences between participant groups and experimental conditions. Each LV consists of a pair of vectors that reflect a symmetrical relationship between the components of the experimental design most

related to differing signals in the voxels on one hand, and the optimal spatial pattern of voxel signals related to the identified design components on the other. The numerical weights at each voxel are called voxel saliences. The saliences identify the collection of voxels that, as a whole, are most related to the effects expressed in the LV. Multiplying the BOLD signal value in each brain voxel for each subject by the salience for that voxel, and summing across all voxels, gives a “brain score” for each subject on a given LV. Brain scores indicate the degree to which each subject shows the spatial pattern of voxels expressed in the LV. The task saliences indicate the degree to which each task is related to the identified pattern of BOLD amplitude differences. Task saliences can be interpreted as the optimal contrast that codes the effect depicted by the voxel saliences. PLS is similar to other multivariate techniques, such as principal component analysis, in that contrasts across conditions or groups typically are not specified by the experimenter. Instead, the algorithm extracts LVs explaining the covariance between groups, conditions and brain activity in order of the amount of covariance explained, with the LV accounting for the most covariance extracted first.

Statistical assessment for PLS is done using permutation tests for the LVs and bootstrap estimation of standard errors for the voxel saliences. The permutation test assesses whether the effect represented in a given LV, captured by the singular value, is sufficiently strong to be different from random noise. The standard error estimates of the voxel weights/salience from the bootstrap tests are used to assess the reliability of the nonzero saliences in significant LVs. No corrections for multiple comparisons are necessary because the voxel saliences are calculated in a single mathematical step on the whole brain. The bootstrap ratio is proportional to a z-score, but should be interpreted as a confidence interval, where we designated a threshold of 4.1 corresponding roughly to a 99.99% confidence interval, or a P value less than 0.0001.

We additionally used task PLS to identify a ROI (i.e., seed voxel) in the MTL whose activity reliably differentiated encoding from baseline tasks. Specifically, from the LV that differentiated brain activation during encoding versus baseline, we chose the voxel within MTL (bilaterally) with the highest bootstrap ratio.

Behavior PLS

Behavior PLS examines the correlations between a behavior measure and the rest of the brain. For the current article, our behavior measure was recognition hit rate. Although it is possible that the MTL seed that best differentiates encoding from baseline tasks also correlates with subsequent recognition performance, this is not invariably the case. To foreshadow, we found that it was true for controls but not for patients, which replicates our previous

univariate findings. Thus, the behavior PLS was performed with only the MCI group, using only the encoding condition. The correlation between hit rate and the rest of the brain was computed across participants during the encoding task, resulting in a matrix containing a within-task brain-behavior correlation map. Singular value decomposition of the brain-behavior correlation matrix produces three new matrices: the singular image of voxel saliences, singular values, and task saliences. The voxel saliences give the spatiotemporal activity pattern for the LV. The correlation between the brain scores (dot-product of the voxel salience and fMRI data) and hit rate indicates the strength of the relationship between the spatiotemporal activity pattern for the LV and hit rate. Statistical assessment is similar to that used for task PLS.

We used the behavior PLS to identify the voxel whose activity changes most reliably correlated with changes in hit rate (i.e., had the highest bootstrap ratio) in the MCI group.

Seed/Behavior PLS

Seed/behavior PLS examines group- and task-dependent correlations between a seed ROI, a behavior measure and the rest of the brain. For the current article, only the encoding task was used in the analyses because we were interested specifically in the functional networks that support encoding and vary with recognition success. Therefore, our two-group/seed/behavior PLSs identified LVs that capture group dependent changes in cortical regions that are functionally connected with a seed voxel during encoding, and also facilitate subsequent recognition (i.e., brain-seed-behavior correlation). The correlation of the behavior measure, the fMRI signal for the seed, and the fMRI signal for the rest of the brain is computed across participants within each group, resulting in a matrix of within-group behavior-seed-brain correlation maps. Singular value decomposition of the behavior-seed-brain correlation matrix produces three new matrices: the singular image of voxel saliences, singular values, and group saliences. The variation across the group saliences indicates whether a given LV represents a similarity or difference in the behavior-seed-brain correlation across groups. This can also be shown by calculation of correlation between the brain scores (dot-product of the voxel salience and fMRI data) and seed fMRI signal or behavior for each task. The voxel saliences give the corresponding spatiotemporal activity pattern.

Our first two-group/seed/behavior PLS explored how the functional connectivity of the right parahippocampal gyrus (identified in the task PLS; see Fig. 1A) changed in relation to subsequent recognition success (as measured by hit rate) and assessed potential group differences in this pattern. The second two-group/seed/behavior PLS analysis explored how the functional connectivity of the right parahippocampal gyrus and left BA 20 (region selected from the preceding behavior PLS with MCI patients; see Fig. 1B) changed in

Figure 1.

Seed voxel locations in three-dimensional view in MNI space. **A:** The parahippocampal seed voxel (MNI coordinate: 28.0, -28.0, -16.0); **B:** The BA 20 seed voxel (MNI coordinate: -44.0, 12.0, -40.0). Brains are displayed according to the neurological convention (L = L).

relation to hit rate across groups. Statistical assessment is similar to that used for task PLS. For these analyses, we designated bootstrap thresholds of 4.1 (confidence interval = 99.99%, or a $P < 0.0001$), or 3.3 (confidence interval = 99.9%, or a $P < 0.001$) as noted in Tables III and IV. We used different bootstrap thresholds to capture visually all the stable voxel clusters that form memory networks, but keep these clusters small enough that they are easy to differentiate.

RESULTS AND DISCUSSION

As anticipated, there was a significant difference between groups in subsequent recognition performance (control mean = 0.85, standard error = 0.043, MCI mean = 0.67, standard error = 0.059, $t(26) = 2.683$, $P < 0.05$). Importantly, there was sufficient variability in performance in both groups that could be exploited to identify networks that facilitate subsequent recognition in the context of MTL damage. Our activity analysis (two-group task PLS) identified one significant latent variable, which differentiated brain activation during encoding versus baseline, and showed that control and MCI groups shared the same pattern of activation (explained covariance = 92.83%, $P < 0.001$, Fig. 2, see Table II for a list of local maxima). Increased encoding-related activity was seen in bilateral visual and fusiform cortex, bilateral parietal cortex, left lateral prefrontal cortex, and right parahippocampal gyrus (with this cluster extending into the hippocampus). Increased baseline-related activity was seen in left medial prefrontal cortex. The extensive activation in visual and fusiform cortex during encoding was likely related to the fact that the pictures presented during encoding varied, while only a single scrambled pattern was presented repeatedly during baseline.

Figure 2.

Singular image (top) and brain scores bar graph (bottom) for LVI in the two-group task PLS. The singular image identifies regions with maximal differentiation between encoding and control conditions for both control and MCI groups, displayed on axial slices from -52 to 80 in MNI atlas space. Brains are displayed according to the neurological convention ($L = L$). Yellow

regions represent increased encoding-related activity, and blue regions represent increased control-related activity. The brain scores bar graph captures the mean brain score for each condition in each group. The error bars indicate the 95% confidence intervals derived from bootstrap estimation.

The lack of any task-related differences in activation patterns between patients and controls may seem surprising at first. Although our original univariate analysis of these data did not indicate a group effect for the hippocampus, there were other regions in which activation differences were observed (e.g., in frontal, temporal, and parietal neo-

cortex; Mandzia et al., 2009). Unlike the univariate analysis, in which we specified contrasts to test for group differences in signal intensity at the voxel level, with PLS we did not specify any a priori contrasts across conditions or groups. Instead, we allowed the algorithm to extract LVs explaining the covariance between groups, conditions

TABLE II. Local maxima from the two-group task PLS

Region	<i>x</i> (mm)	<i>y</i> (mm)	<i>z</i> (mm)	BSR
Medial frontal gyrus (BA 6)	−4	24	68	5.92
Inferior frontal gyrus (BA 44)	−44	12	24	6.22
Inferior frontal gyrus (BA 45)	−48	36	8	5.73
Inferior frontal gyrus (BA 47)	−44	36	−28	8.60
Middle frontal gyrus (BA 46)	48	20	28	5.96
Middle frontal gyrus (BA 6)	−32	12	60	5.55
Middle frontal gyrus (BA 9)	−40	28	48	4.76
Middle frontal gyrus (BA 11)	36	48	−20	5.60
Thalamus	0	−12	0	4.87
Parahippocampal gyrus	28	−28	−16	4.55
Fusiform gyrus (BA 37)	36	−44	−24	10.01
Inferior parietal lobe (BA 40)	−28	−68	44	8.24
Superior parietal lobe (BA 7)	32	−76	44	6.59
Fusiform gyrus (BA 18)	−44	−76	−20	10.54
Lingual gyrus (BA 18)	12	−52	0	5.05
Middle occipital gyrus (BA 19)	40	−84	−4	7.56
Superior occipital gyrus (BA 19)	−28	−84	24	9.83
Cerebellum	40	−84	−24	10.26

Local maxima were determined at $P < 0.0001$. Regions indicate the gyral locations and BA of the cluster peak. MNI coordinates were converted into Talairach coordinates using the mni2tal script (http://eeg.sourceforge.net/mridoc/mri_toolbox/mni2tal.html). Gyral locations and BA were then determined by reference to Talairach and Tournoux (1988). *x*, *y*, and *z* indicate voxel coordinates in MNI space. BSR represents each voxel's PLS parameter estimate divided by its standard error.

and brain activity in order of the amount of covariance explained, with the LV accounting for the most covariance extracted first. Our only significant LV (explaining 92.83% of the covariance) indicates that differences in brain activation between encoding and baseline conditions, not differences between groups, accounted for the most covariance in our data. Our findings also contrast with studies demonstrating hyper- versus hypoactivation in medial temporal and other regions as a function of degree of clinical impairment (e.g., Celone et al., 2006). Without a larger number of MCI patients, we are unable to look for subgroups within our data, so this discrepancy may be more apparent than real. Nonetheless, as our principle interest in this study was to assess the relationships between brain activation patterns and memory performance, we consider it an advantage that the overall task pattern was indistinguishable between our groups.

We next used seed/behavior PLS to identify group- and task- dependent changes in the cortical regions that were functionally connected with the MTL and also supported good memory performance. This may seem an unusual approach, but it is the most direct means of identifying a pattern of activation that relates to performance variability without constraining the expected relationship to a single brain region. In our previous article [Mandzia et al., 2009],

we examined whether the spatial extent of activated voxels in hippocampus and parahippocampal gyrus correlated with subsequent recognition performance (i.e., hit rate), and found a significant correlation in controls but not in MCI patients. Thus, we focused our current analysis on the hippocampal or parahippocampal voxel that most stably differentiated encoding from baseline conditions as identified in the two-group task PLS. This voxel was located in the right parahippocampal gyrus (MNI coordinate: 28.0, −28.0, −16.0).

The two-group/seed/behavior PLS with the right parahippocampal seed and hit rate identified one significant latent variable, which depicted one encoding network that did not vary by group, with correlated activation in MTL and several neocortical regions. This network facilitated subsequent recognition for healthy controls but not MCI patients (explained covariance = 46.23%, $P < 0.05$, Fig. 3, see Table III for a list of local maxima). In controls, the positive saliences, indicating a positive correlation with the right parahippocampal seed and hit rate, included bilateral hippocampus and parahippocampal gyrus, as well as temporal, frontal, and parietal cortical regions. Negative saliences were anticorrelated to encoding network activation. These regions, primarily lateral temporal cortex and inferior prefrontal cortex, showed greater activity when the encoding network was suppressed and recognition performance was poor. In MCI patients, the parahippocampal seed showed reliable correlations with the encoding network described for the controls, indicating that functional connectivity in this network is intact. Activation in this network very likely supports encoding in MCI patients to some degree, but it does not account for variation in their task performance, as the correlation with hit rate was not stable. Overall, these findings concur well with our univariate findings for the medial temporal regions [Mandzia et al., 2009].

Because the parahippocampal encoding network did not account for variation in subsequent recognition for MCI patients, and these patients were performing above chance in our recognition task, we hypothesized that they were using an alternate network to support good memory encoding. To identify the alternate network, we performed a behavioral PLS with hit rate for MCI patients alone. Although this analysis did not identify any significant LVs, indicating that we could not interpret a whole-brain pattern, there were some highly reliable voxels (by bootstrap estimation) and we chose that voxel whose activity changes most reliably correlated with changes in hit rate. This voxel was located in left inferior temporal cortex, in BA 20 (MNI coordinate: −44.0, 12.0, −40.0). To confirm that BA 20 activation during deep encoding predicted hit rate during the retrieval of deeply encoded items in MCI patients, we calculated the coefficient of determination (R -squared) between these variables. As expected, the relationship was significant exclusively for the MCI group (MCI $R^2 = 0.76$ $P < 0.0001$; control $R^2 = 0.02$, $P = 0.63$). Although this does not form part of the

Figure 3.

Singular image (top) and correlation bar graph (bottom) for LVI from the two-group/parahippocampal seed/hit rate PLS. The correlation bar graph captures the group-dependent changes in the correlation with the seed voxel and behavior of the areas identified in the singular image. The error bars indicate the 95% confidence interval derived from bootstrap estimation. When the error bar crosses zero (as it does for hit rate in the MCI group), it indicates that the correlation between behavior and the areas identified in the singular image is nonreliable. The singular image shows brain-seed and brain-behavior correlations for both control and MCI groups, displayed on axial slices from

–52 to 80 in MNI atlas space. Brains are displayed according to neurological convention (L = L). For controls, regions in yellow demonstrate reliable positive correlations with the right parahippocampal seed and with hit rate. Regions in blue are anticorrelated to the encoding network activation and to hit rate. For MCI patients, regions in yellow also show reliable correlations with the right parahippocampal seed. However, this network does not support effective encoding, as there is no reliable correlation with hit rate. Regions in blue are anticorrelated to encoding network activation.

TABLE III. Local maxima from the two-group/parahippocampal seed/hit rate PLS

Region	x (mm)	y (mm)	z (mm)	BSR
Superior frontal gyrus (BA 8)	24	32	60	7.23
Caudate	-20	8	20	8.02
Postcentral gyrus (BA 2)	40	-20	24	4.97
Middle temporal gyrus (BA 21)	64	-8	-8	6.77
Middle temporal gyrus (BA 37)	60	-68	4	6.02
Superior temporal gyrus (BA 22)	44	-48	20	6.15
Thalamus	-48	-24	4	6.07
Thalamus	16	-32	12	6.55
Hippocampus	28	-28	-16	16.76
Parahippocampal gyrus	-20	-24	-24	9.17
Inferior parietal lobe (BA 40)	-48	-72	36	5.67
Inferior parietal lobe (BA 40)	-24	-44	56	6.11
Superior parietal lobe (BA 7)	32	-76	56	6.21
Precuneus (BA 7)	-12	-72	60	5.94
Cuneus (BA 18)	-4	-84	16	5.73
Cerebellum	4	-44	-52	7.38
Cerebellum	32	-84	-40	5.05
Middle temporal gyrus (BA 21)	-60	-36	0	-6.89

Local maxima were determined at $P < 0.0001$. Regions indicate the gyral locations and BA of the cluster peak. MNI coordinates were converted into Talairach coordinates using the mni2tal script (http://eeg.sourceforge.net/mridoc/mri_toolbox/mni2tal.html). Gyral locations and BA were then determined by reference to Talairach and Tournoux (1988). x , y , and z indicate voxel coordinates in MNI space. BSR represents each voxel's PLS parameter estimate divided by its standard error.

“canonical” encoding network observed in controls, there is a plausible anatomic linkage as diffusion tensor imaging confirms a direct connection between parahippocampal gyrus and anterior temporal lobe via the inferior occipitofrontal fasciculus [Powell et al., 2004]. There are some clues as to its functional significance in our data as BA 20 has been shown to be involved in responsive naming tasks [Tomaszewski Farias et al., 2005], in visual short-term memory [Sugase-Miyamoto et al., 2008] and object vision [Tanaka, 1996; Ungerleider et al., 2008; Zhong and Rockland, 2004]. This region's strong correlation with hit rate in MCI patients suggests that those patients with better recognition scores were invoking additional processes to aid themselves in making the natural/man-made decision during the encoding task, like naming the objects to be remembered, or focusing on the visual features of the pictures presented.

We used two-group/seed/behavioral PLS to explore how the functional connectivity of our BA 20 seed and the parahippocampal seed from the previous analysis changed in relation to hit rate across groups. This analysis identified two significant LVs which jointly showed that subsequent recognition is supported by different networks in MCI and normal controls. The first LV (explained covariance =

42.29%, $P < 0.001$, Fig. 4, see Table IV for a list of local maxima) reinforced what we found in our previous two-group/seed/behavior PLS, that an encoding network with correlated activation in MTL and neocortical regions is activated during encoding for both patients and controls, and accounts for variation in subsequent recognition for controls but not for MCI patients. For the controls, introducing BA20 into the connectivity analysis showed that increased activity in BA 20 is negatively correlated with activation of the MTL network and with recognition success. In contrast, for MCI patients, activity in BA 20 was positively correlated with MTL network activation, suggesting that it was involved in the encoding process for that group. However, the network identified in LV1 did not explain variations in subsequent recognition amongst MCI patients.

An alternative network supporting subsequent recognition in the MCI patients was pulled out by the second significant LV from the two-group/BA 20 and parahippocampal seed/behavioral PLS. Specifically, LV2 showed BA 20 connections that were associated with subsequent recognition success in MCI patients, as well as additional parahippocampal connections that were associated with recognition success in normal controls (explained covariance = 31.95%, $P < 0.05$, Fig. 5, see Table IV for a list of local maxima). For MCI patients, positive correlations, located primarily in temporal cortex and lateral prefrontal cortex, demonstrated reliable relationships with the left BA 20 seed and hit rate. For controls, positive correlations, located primarily in bilateral temporal pole, demonstrated reliable relationships with the right parahippocampal gyrus seed and with hit rate.

Our results indicate that despite MTL damage, MCI patients can activate the MTL encoding network. While activation here accounts for encoding success in controls, recruitment of additional regions, identified by the BA 20 pattern, is required to explain variation in MCI performance. We propose that the BA 20 pattern represents functional reorganization caused by reduced efficiency in the “typical” MTL encoding network. In concordance with this hypothesis, several ageing studies have shown compensatory functional reorganization [Della-Maggiore et al., 2000; Grady et al., 2003a, 2005, in preparation; McIntosh et al., 1999]. For example, Cabeza et al. [2002] measured activity in prefrontal cortex for younger adults, low-performing older adults and high-performing older adults while they performed recall and source memory tasks. Compared to recall, source memory was associated with right prefrontal activations in younger adults and low-performing older adults, but bilateral prefrontal activations in high-performing older adults. Thus, a reduction in hemispheric asymmetry was found in high-performing but not in low-performing older adults. The authors concluded that low-performing older adults recruited a similar network as young adults but used it inefficiently, whereas high-performing older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks. Similarly, Grady et al. [2003a] showed

Figure 4.

Singular image (top) and correlation bar graph (bottom) for LVI from the two-group/parahippocampal and BA 20 seed/hit rate PLS. The correlation bar graph captures the task-dependent changes in the correlation with the seed voxels and behavior of the areas identified in the singular image. The error bars indicate the 95% confidence interval derived from bootstrap estimation. When the error bar crosses zero (as it does for hit rate in the MCI group), it indicates that the correlation with behavior and the areas identified in the singular image is nonreliable. The singular image shows brain-seed and brain-behavior correlations for both control and MCI groups, displayed on axial slices from

−52 to 80 in MNI atlas space. Brains are displayed according to neurological convention (L = L). For controls, regions in yellow are positively correlated with the parahippocampal seed and with hit rate, and negatively correlated with the BA 20 seed. Regions in blue are negatively correlated with the parahippocampal seed and with hit rate, and positively correlated with the BA 20 seed. For MCI patients, regions in yellow are positively correlated with the parahippocampal and BA 20 seeds, but show no reliable relationship with hit rate. Regions in blue are negatively correlated with the parahippocampal and BA 20 seeds.

TABLE IV. Local maxima from the two-group/parahippocampal and BA 20 seed/hit rate PLS

Region	x (mm)	y (mm)	z (mm)	BSR
LV1				
Superior frontal gyrus (BA 8)	36	32	56	5.82
Inferior temporal gyrus (BA 20)	-64	-12	-24	5.94
Middle temporal gyrus (BA 21)	68	-12	-16	6.63
Middle temporal gyrus (BA 21)	44	-44	8	5.63
Middle temporal gyrus (BA 37)	56	-64	8	6.27
Superior temporal gyrus (BA 22)	-48	-24	4	6.24
Hippocampus	24	-28	-16	9.97
Parahippocampal gyrus	-24	-24	-20	7.06
Inferior parietal lobe (BA 40)	44	-24	24	5.21
Inferior parietal lobe (BA 40)	-48	-72	40	6.00
Superior parietal lobe (BA 7)	-8	-72	56	5.36
Cingulate (BA 31)	-4	-40	32	6.00
Cuneus (BA 18)	0	-80	16	6.03
Cerebellum	36	-80	-44	5.41
Cingulate (BA 32)	12	40	16	-5.36
LV2				
Inferior frontal gyrus (BA 45)	-60	28	12	4.99
Middle frontal gyrus (BA 6)	36	20	60	4.32
Middle frontal gyrus (BA 11)	-48	56	-12	5.45
Superior frontal gyrus (BA 10)	-28	64	16	4.30
Middle temporal gyrus (BA 39)	56	-76	16	4.31
Superior temporal gyrus (BA 22)	72	-36	8	5.84
Superior temporal gyrus (BA 38)	-44	12	-40	11.08
Cerebellum	-4	-48	-8	6.49
Cerebellum	52	-56	-28	4.24
Inferior frontal gyrus (BA 47)	32	40	-8	-6.61
Inferior frontal gyrus (BA 47)	-36	24	0	-5.12
Middle frontal gyrus (BA 11)	-36	48	-20	-5.36
Middle frontal gyrus (BA 6)	20	4	56	-4.62
Cingulate (BA 32)	12	12	44	-6.17
Precentral gyrus (BA 6)	-64	0	32	-5.07
Precentral gyrus (BA 6)	40	-12	40	-5.36
Postcentral gyrus (BA 2)	-64	-24	44	-4.82
Postcentral gyrus (BA 2)	40	-20	56	-5.27
Superior temporal gyrus (BA 21)	-52	0	-12	-6.74
Superior temporal gyrus (BA 38)	52	8	-8	-6.98
Thalamus	8	-8	16	-5.54
Cingulate	16	-12	-12	-4.39
Hippocampus	-16	-12	-12	-5.73
Paracentral lobe (BA 5)	-8	-40	68	-6.73
Inferior parietal lobe (BA 40)	36	-32	32	-3.72
Superior parietal lobe (BA 7)	-32	-44	64	-4.77
Cingulate (BA 23)	-20	-24	28	-4.22
Cingulate (BA 30)	-20	-48	20	-4.74

Local maxima were determined at $P < 0.0001$ for LV1, and $P < 0.001$ for LV2. Regions indicate the gyral locations and BA of the cluster peak. MNI coordinates were converted into Talairach coordinates using the mni2tal script (http://eeg.sourceforge.net/mridoc/mri_toolbox/mni2tal.html). Gyral locations and BA were then determined by reference to Talairach and Tournoux (1988). x , y , and z indicate voxel coordinates in MNI space. BSR represents each voxel's PLS parameter estimate divided by its standard error.

that older adults whose memory performance was identical to younger adults recruited bilateral prefrontal cortex whereas the younger adults activated only the right prefrontal regions. A subsequent study by Grady et al. [2003b] demonstrated engagement of a compensatory network in patients with AD that, consistent with our results, involved bilateral frontal and parietal regions. Activation of this network was correlated with better performance in the patient group. Our findings demonstrate for the first time a similar pattern in MCI, in that recruitment of an alternate network is required to explain performance.

LIMITATIONS

There are several limitations to these findings. First, there are rather few data points included in our analyses. Although it would have been advantageous to have more data to explore, this is a secondary analysis of data collected as part of a larger, already published study. Importantly, we are not concerned about type II error in our comparison of patients and controls because we found significant group differences in functional connectivity in the current article using multivariate analyses, and in activity in the previously published article using univariate analyses. Another limitation is the use of hit rate rather than a "purer" measure of recognition sensitivity (i.e., d' -prime) as our behavioral score; we elected to do this because the d' -prime data for patients were excessively noisy (i.e., standard deviation greater than the mean). However, our use of hit rate leaves open the possibility that the behavioral score may be contaminated by bias. For this to be the case, one would have to assume a link between degree of BA 20-network activation and likelihood of bias in a subsequent recognition, which is implausible. However, to check on this possibility, we ran a two-group/seed/behavioral PLS analysis with the BA 20 and parahippocampal seeds using false alarms rather than hit rate as the behavioral measure. We found no reliable behavioral correlations in that analysis. We also note that the only other article correlating functional connectivity analysis with recognition memory performance in MCI patients also used hit rate [Celone et al., 2006].

CONCLUSIONS

In the absence of complete damage to a critical node, the canonical encoding network can activate normally, but this activation may not be sufficient to facilitate good recognition performance. Other regions must be incorporated into this network to account for variations in memory performance. Our findings add to a growing body of research demonstrating that relating fMRI data to clinically relevant memory impairment requires elucidating

Figure 5.

Singular image (top) and correlation bar graph (bottom) for LV2 from the two-group/parahippocampal and BA 20 seed/hit rate PLS. The correlation bar graph captures the task-dependent changes in the correlation with the seed voxels and behavior of the areas identified in the singular image. The error bars indicate the 95% confidence interval derived from bootstrap estimation. When the error bar crosses zero (as it does for the BA 20 seed in the control group and the PHC seed in the MCI group), it indicates that the correlation with the seed voxel and the areas identified in the singular image is nonreliable. The singular image shows brain-seed and brain-behavior correlations for both

control and MCI groups, displayed on axial slices from -52 to 80 in MNI atlas space. Brains are displayed according to neurological convention (L = L). For controls, regions in blue demonstrate reliable correlations with the right parahippocampal seed and with memory success. Regions in yellow are anticorrelated with the parahippocampal network supporting performance. In MCI patients, regions in yellow are positively correlated with activity in BA 20 and hit rate. Regions in blue are anticorrelated with the BA 20 seed, suggesting that increased activity in these regions is associated with a suppression of the BA 20 encoding network, and is detrimental for memory performance.

connectivity patterns and linking those directly to behavior.

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