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Effect of Disease Severity on Neural Compensation of Item and Associative Recognition in Mild Cognitive Impairment

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Abstract. It is proposed that the prodromal phase of Alzheimer's disease is associated with additional brain activation in key regions involved in memory, reflecting compensatory brain plasticity. Very little is known, however, about the evolution of these compensatory mechanisms as the brain acquires more damage. We conducted an fMRI memory study measuring brain activation related to old/new (item recognition) and intact/rearranged (associative recognition) word-pair recognition paradigms in 26 persons with mild cognitive impairment (MCI) and 14 healthy older adults. The Mattis Dementia Rating Scale was used to divide persons with MCI into those with higher and lower cognitive performances. Results indicated more brain activation in MCIs than in controls but disease severity determined which cognitive process was associated with larger activation: Persons with less severe MCI showed hyperactivation during associative recognition only, whereas persons with more severe MCI showed hyperactivation during item recognition only. These hyperactivations were found mainly in brain areas that are typically associated with retrieval mode (e.g., bilateral prefrontal cortex). These findings indicate that neural plasticity occurs during the entire MCI phase but that it is associated with different cognitive components. As they progress in the disease, individuals with MCI will experience a breakdown in the compensatory mechanisms for associative recognition accompanied by emergence of compensatory mechanisms for item recognition.

Keywords: Alzheimer's disease, cognition, episodic memory, functional magnetic resonance imaging

INTRODUCTION

An important feature of Alzheimer's disease (AD) is that the associated brain lesions and the resulting cognitive deficits are progressive [1]. Yet, and surprisingly, little is known regarding the evolution of the functional brain response to these growing damages. Most studies assumed that their mild cognitive impairment (MCI) participants were equivalent in terms of disease severity and treated them as a single homogeneous group on this dimension. This strategy has been useful in providing a nomenclature of the pattern of cognitive impairment those patients experience. However, it does not provide information regarding the dynamics of the brain-behavior relationship as the brain loses healthy neurons. This might be a major shortcoming because the recent literature on brain plasticity suggests that cerebral insult results in substantial plasticity and reorganization even in the aging brain [2, 3]. Because lesions are progressive, the AD brain might attempt neural compensatory mechanisms, particularly during the first stages of the disease while it still has sufficient resources, and these might be successful. If true, disease severity should have a profound impact on the pattern of functional activation associated with different cognitive tasks. The major goal of

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this study was to provide the empirical data to address this important question.

The idea that the functional brain activation changes as the brain acquires more pathology in neurodegenerative diseases is contained in a number of integrative models of cerebral activation [4–7]. For example, Prvulovic and collaborators [8] have suggested that the brain damage characteristic of the earliest phase of AD decreases processing efficiency in mildly affected brain areas while preserving their processing capacity. As a result, regions that are only mildly impaired should have sufficient neuronal resources to allow the implementation of compensatory mechanisms relying on increased neuronal recruitment and brain activation. This would result in the hyperactivation of mildly affected brain regions in patients relative to controls when compared using functional brain imaging techniques. However, as the disease advances, increasing damage to the affected brain regions results in a decrement in processing efficiency and capacity, impeding neuronal recruitment and compensatory mechanisms. This inability to compensate should be associated with hypoactivation. The pattern of brain functional activation in AD may therefore be characterized by a dynamic shift from normal to hyper- to hypoactivation as the disease progresses and extends to different brain areas. There are also predictions regarding the brain areas that should reflect hyper and hypoactivation. In the early compensation phase, hyperactivation should be found in areas that are mildly affected by the disease and that are typically recruited by the cognitive task. It is also expected that hyperactivation occur in alternative areas that might be used to support compensation [9, 10]. Later in the disease, hypoactivation should be found in disease-affected areas that are recruited for the cognitive task. This dynamic view of brain activation in neurodegenerative diseases holds considerable promise for understanding severity-related activations in AD.

Our predictions are expected to be particularly relevant for brain activations related to episodic memory, as it is one of the first cognitive functions to be impaired in early AD [11, 12] and the main domain of subjective cognitive complaints [13]. The neural substrates of episodic memory have been studied extensively (for review, see [14]), but very little is known about how these memory networks are modified as the brain acquires new pathologies. Furthermore, and as mentioned above, neural compensation depends not only on disease severity, but also on the task demands and characteristics. As different components are impaired at different phases during the disease, they should benefit differently from compensation during the course of their progression. This is relevant here as different components of episodic memory retrieval are dependent on different brain regions and thus impaired in different sequences during the disease process. This is the case for the distinction between recollection and familiarity processes. Recollection refers to the retrieval of qualitative information about a specific study episode [15]. Recollection tasks require that participants retrieve contextual details about the event or item. In turn, familiarity refers to the retrieval of events/items experienced without their contextual details. In familiarity tasks, participants only need to determine whether they have experienced the item recently, without recalling its detailed context. One of the methods that have been used to dissociate familiarity and recollection processes is to compare associative recognition to single-item recognition (familiarity). Item recognition is a task that can be done by relying solely on familiarity whereas associative recognitive would necessitate recollective processes [16, 17]. Though this distinction is the subject of some debate, it is supported by many arguments including experimental dissociations, neuropsychological dissociations, and evidence from brain imaging that the two processes activate different brain regions [18]. Many studies have shown that recollection is severely impaired in AD but that familiarity is not as affected by the disease in the early stages [19, 20]. Accordingly, it has been suggested that associative recognition is altered in persons with MCI, whereas item recognition is impaired later when persons meet criteria for AD [21–23; but see 24]. The plasticity model predicts that the extent of damage in a process-related network will determine its potential for compensation. In this model, compensation only arises when mild damage is present. Thus, it can be predicted that persons with less severe MCI will show more neural compensation for associative recognition than for item recognition, since the associative recognition network is impaired at this stage and lesions are mild enough to allow brain plasticity to occur. By contrast, persons with more severe MCI should show neural compensation only for item-recognition because impairment to the associative recognition network is too severe to allow compensation (Fig. 1).

These predictions were tested using a median split of Mattis Dementia Rating Scale (MDRS) scores to divide degrees of MCI. The assumption was that individuals with lower scores were in a more advanced phase of the disease and/or experienced a larger degree of brain pathology than persons with higher scores. We

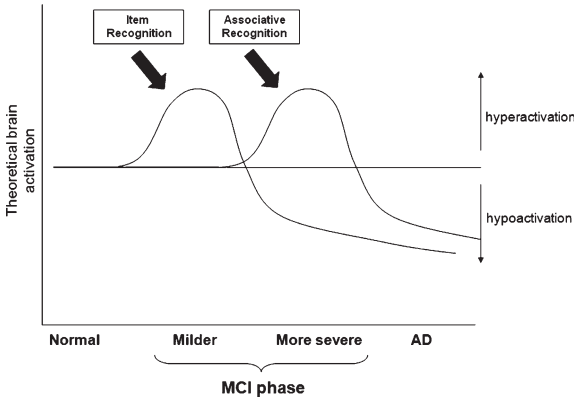

Fig. 1. Progression of theoretical brain activation for item recognition and associative recognition in normal individuals and patients with milder mild cognitive impairment (MCI), more severe MCI, and Alzheimer's disease (AD).

tested the effect of severity on brain activation and compensation using a word-pair associative recognition procedure with two retrieval conditions: an item recognition and an associative recognition. We predicted that persons with less severe MCI would show neural compensation during associative recognition only, whereas those with more severe MCI would show neural compensation during item recognition only.

In terms of brain activation, these neural compensatory mechanisms were predicted to manifest as hyperactivation (i.e., more activation in MCI than healthy controls) in key regions involved in episodic memory retrieval. It is proposed that the neural substrates measured when using recognition in a block design reflects retrieval mode to a large extent as it reflects brain changes over a relatively large temporal frame [25, 26]. Retrieval mode refers to a cognitive set that the participant engages in to ensure that the stimuli are processed as episodic retrieval cues. The processes involved during this mode have been associated mainly with prefrontal activation [27]. As item recognition involves both familiarity processes and retrieval mode, and since associative recognition involves both recollection processes and retrieval mode, presence of prefrontal hyperactivation was therefore expected for both tasks. In addition, we expect hyperactivation in brain areas that have been identified as being involved in memory-related compensatory mechanisms in older adults. For instance, prefrontal regions contralateral to the ones usually activated by episodic memory tasks have been identified as compensatory structures in "high-performing" older adults [28]. Also, the dorsolateral prefrontal cortex is known to increase its activation following attentional training in healthy older adults, suggesting an involvement of this area in compensatory mechanisms [29]. A shift from hyperactivation (see Fig. 1) associated with a memory process affected early (associative recognition) to hyperactivation associated with a memory process affected later (item recognition) would reflect the compensation breakdown for associative retrieval and emergence of compensation for item retrieval during the MCI phase. These hyperactivations should be found mainly in the memory-associated regions mentioned above. Thus, plastic changes are predicted to involve different cognitive processes as brain dysfunction develops in MCI. Investigating the relationship between cognitive severity and fMRI brain activation patterns in this population will provide crucial new information regarding the dynamic nature of the brain/behavior relationship and will allow a better understanding of compensatory mechanisms in age-related cognitive disorders.

MATERIALS AND METHODS

Participants

Forty participants, 26 persons with MCI and 14 healthy older adults, took part in this study. Participants with MCI were recruited from memory clinics and met the criteria for single- or multiple-domain amnestic MCI [11, 30, 31]: (1) they expressed a concern regarding their memory; (2) they performed at least 1.5 standard deviation (SD) below the average level of persons of similar age and education on standardized memory tests; (3) they showed no global cognitive impairment on the basis of the Mini-Mental State Examination (MMSE, adjusted for age and education); and (4) they showed no significant impact on daily functions as measured by the SMAF (Functional Autonomy Measurement System) functional impairment scale and clinical interview. Persons with MCI completed an extensive neuropsychological evaluation that covered episodic memory (Rappels Libres/Rappels indicés-16, RL/RI-16, free and cued word recall task [32, 33]; Batterie d'Efficience Mnésique, BEM, text memory [34]; and 20-min recall of the Rey's Complex Figure [35]), executive functions (third plate of Stroop-Victoria [36]; and copy of Rey's Complex Figure [35]), visuospatial processing (Benton Judgment of line orientation [37]), speed of information processing (Coding of the WAIS-III [38]), language (Boston Naming Test [39]), and global cognitive functions (Mattis Dementia Rating Scale, MDRS [40]; and MMSE [41]). Participants with MCI also underwent an extensive medical,

neurological, and neuroradiological examination to exclude the presence of any other significant systemic, neurological, or psychiatric condition that could explain their cognitive difficulties.

A median split of the MDRS [40] scores was used to separate participants with MCI into two groups: those with a higher level of overall cognitive functioning (MCI higher-cognition, $n = 13$) and those with a lower level of overall cognitive functioning (MCI lower-cognition, $n = 13$). The MDRS was preferred over the MMSE [41] as a measure of severity because participants with MCI show less of a ceiling effect on this scale; thus, it has the variability necessary to use a median split. In addition, the MDRS may be more sensitive to the milder cognitive impairments of those with MCI, as it investigates a broader range of cognitive functions.

Participants with MCI were followed over a two-year period after their participation in this study. At the two-year follow-up, no one in the MCI higher-cognition group met criteria for AD. Of the same group, seven had remained stable, and six showed a cognitive decline insufficient to meet criteria for AD. Over the same period, four in the MCI lower-cognition group remained stable, one showed cognitive decline insufficient for AD, and eight were diagnosed with AD. Patients with AD were diagnosed according to the NINCDS-ADRDA [42] and DSM-IV criteria [43].

Healthy older adults also completed an abbreviated clinical and neuropsychological assessment involving measures of global cognitive functions (MDRS,[1] MMSE), speed of information processing (Coding subtest of the WAIS-III [38]), and episodic memory (a cued and free word recall task: RL/RI-16 [32]) to ensure they did not suffer from cognitive deficits. The study was approved by an ethics committee: le Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec (CMER-RNQ).

Data acquisition

Magnetic resonance imaging (MRI) was performed using a SIEMENS 3T Magnetom TRIO System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut Universitaire de Gériatrie de Montréal. For high anatomical resolution, a sagittal T1-weighted three-dimensional MPRAGE sequence was obtained at the end of the two runs (TR/TE = 1950/3.93 ms, flip angle = 15°; 176 slices, voxel size = $1 \times 1 \times 1$ mm, field of view = 256 mm, matrix = 256×256). Functional MR images were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90°; 31 interleaved slices, voxel size = $3.75 \times 3.75 \times 5$ mm with a gap of 1 mm, field of view = 240 mm, matrix = 64×64).

Task procedure

Participants were asked to memorize lists of nine concrete word pairs. There were 16 lists to learn in total and each list was learned and tested sequentially. Eight lists were made of word pairs that were semantically related (e.g., butter–cheese), and eight were made of word pairs that were semantically unrelated (e.g., tire–game). Related pairs were created by selecting an item and one of its associates from French lists of semantic associates [44, 45]. Only the second, third, or fourth associates of selected words were chosen to avoid participants guessing and to avoid the encoding of the two words as a single concept. Lists of unrelated word pairs were created by selecting pairs of words with no semantic relation and by ensuring that no words were semantically associated with other items in the list. Words in the lists were one- or two-syllable long. The lists were matched in terms of average word frequency and average word length.

A recognition phase followed learning of each list. In that phase participants performed a yes/no recognition judgment on lists of eight word pairs. This was done under one of two conditions (*old/new* versus *intact/rearranged*). In the *old/new judgment* condition, word pairs in the recognition list were either old (i.e., a pair had been learned during the encoding phase; e.g., tire–game, from the above example) or new ones (i.e., the pair was made of one word presented during the encoding phase and one completely new word; e.g., cheese–milk from the above example). There were as many old as new pairs and those were presented in random order. Of the eight word pairs, half were presented in the same format as during the study phase (e.g., tire–game), and the other half were presented in a reversed format (e.g., game–tire) to ensure participants did not learn only the second word to achieve the task. In the *intact/rearranged judgment* condition, the recognition list was composed of either intact (i.e., a pair had been learned during the encoding phase; e.g., butter–cheese from the above example) or rearranged pairs (i.e., a pair made of two words that were presented during the encoding phase but as member of different pairs; e.g., butter–tire from the above example). Again,

[1] Five healthy controls did not undergo the MDRS.

half of the word pairs were presented in the same format as during the encoding phase (e.g., butter–cheese), and the other half were presented in a reversed format (e.g., cheese–butter) and order of presentation in the list was random. To prevent participants from retrieving items from their short-term memory, at least four word pairs separated the presentation of a pair in the study phase from its presentation in the recognition phase. All lists were equivalent in terms of word frequency and semantic relatedness.

Subjects performed the memory task in two runs. Each run was composed of four alternating series of visual fixation (20 s), encoding (40 s), and recognition (44 s). Therefore, the sequence was: visual fixation – encoding of List 1 (nine pairs, e.g., butter-cheese) – recognition for List 1 (e.g., cheese-milk, for item recognition) – visual fixation – encoding of List 2 (nine new pairs, e.g., tire-game) – recognition for List 2 (e.g., butter-game, for associative recognition) – and so on and so forth until the eight lists were tested. The same procedure was used for item recognition and associative recognition. Each recognition list consisted of either only old/new judgment or only intact/rearranged judgments. During the encoding phase, word pairs were visually presented at a rate of 4 s per pair and mirror projected to participants while they were in the fMRI scanner. Participants were asked to memorize both words of the pairs and to memorize that they were presented "together".[2] During the recognition phase, word pairs were visually presented at a rate of 5 s per pair and participants indicated whether the complete pair had been seen in the study phase or not using a two-button response box. Emphasis was placed on the fact that a positive answer should be provided when the two words were seen as a pair. These instructions were the same for the two recognition conditions. Thus, a "yes" response would be provided for old (in the old/new condition) and intact (in the intact/rearranged condition) pairs, and a "no" response would be provided for new (in the old/new condition) and rearranged (in the intact/rearranged condition) pairs. Visual fixation consisted of fixating a crosshair on the screen. Brief instructions (4 s) were presented prior to each recognition run. The order of presentation of the old/new lists and the intact/rearranged lists was randomized and fixed across participants.

[2] Note that brain activation was recorded during the study phase and that data are being reported in a separate paper [47]. It was found that MCI higher-cognition showed hyperactivations in prefrontal areas whereas the MCI lower-cognition did not show these hyperactivations and even showed hypoactivations in posterior regions.

fMRI procedure

The task was programmed on E-prime, and stimuli were visually presented and mirror projected. Goggles appropriate for MRI scanning were used to correct the vision of the subjects when needed. An fMRI block design paradigm was preferred over an event-related one to maximize detection power [46] and to be more suitable for patients with memory difficulties, as the conditions alternate less frequently in a block design. One week prior to scanning, participants were familiarized with the fMRI procedure and the tasks, using a simulator that mimics the entire fMRI environment.

Image processing and data analysis

Before statistical analysis, functional images were converted into Analyze format and unwarped. Functional volumes from each subject were then realigned to the first acquired volume in the session, and a mean realigned volume was created for each subject. All the realigned volumes from each subject were spatially normalized into Montreal Neurological Institute (MNI) stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 208 s. The instruction blocks were modeled as a condition of no interest. A single-subject analysis was carried out to evaluate the individual contrasts (old/new judgment versus visual fixation, intact/rearranged judgment versus visual fixation) for each subject. A random effect (RFX) analysis was then performed on the contrast images with a two-way analysis of covariance (ANCOVA) using Group (healthy older adults, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (old/new judgment, intact/rearranged judgment) as a within-subject factor, with non-sphericity correction, replications over subjects, and correlated repeated measures. Also, the mean performance (%) of each subject on the task was used as a covariate (see below). *T*-tests were thus performed on the contrast of each task (Recognition old/new > visual fixation & Recognition intact/rearranged > visual fixation) for each group individually (within-group analyses) as well as between the groups (between-group analyses). In addition, *t*-tests were performed between the old/new condition and the intact/rearranged condition for the healthy control group. Within-group analyses were performed using a threshold of $p < 0.05$, family-wise corrected (FWE) with 10 contiguous voxels. Between-group analyses were performed with a more liberal threshold

of $p < 0.001$ (uncorrected, with 5 contiguous voxels) in accordance with what has been used most frequently in the MCI fMRI literature [e.g., 48–51]. All preprocessing and statistical analyses were performed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/).

RESULTS

Sociodemographic and clinical data

Table 1 shows the sociodemographic data and the results of the neuropsychological evaluation for all three groups. The MDRS score of MCI participants (ranged from 117 to 144, mean = 134.61, SD = 6.03, skewness = −0.81) was used to assign each MCI person to either the MCI higher- or lower-cognition groups. One-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor indicated the groups did not differ in age ($F_{(2,37)} = 0.15$, NS) or education ($F_{(2,37)} = 0.64$, NS). In addition, chi-square analyses indicated a similar male-to-female ratio in the three groups ($\chi^2 = 0.05$, $\chi^2 = 0.03$ and $\chi^2 = 0.16$ for the comparison between healthy controls and MCI higher-cognition, healthy controls and MCI lower-cognition, and MCI higher-cognition and MCI lower-cognition, respectively, all NS).

One-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor were also computed on cognitive measures followed by Tukey's post hoc test to determine the source of the effect (Table 1). As expected, both MCI groups showed lower episodic memory capacities than healthy controls (i.e., lower score on the RL/RI-16 test for both groups and lower score on the delayed recall of Rey's Figure for the MCI lower-cognition group), and MCI lower-cognition showed lower episodic memory performances than MCI higher-cognition.

The number of persons meeting criteria for single- or multiple-domain amnestic MCI was also compared across groups. The MCI higher-cognition group comprised five persons with single-domain amnestic MCI and eight persons with multiple-domain amnestic MCI, whereas the MCI lower-cognition group comprised four persons with single-domain amnestic MCI and nine with multiple-domain amnestic MCI. These numbers were equivalent ($\chi^2 = 0.17$, NS).

Behavioral data

The behavioral data obtained from the recognition test are shown in Table 2. A two-way ANOVA with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (old/new judgment, intact/rearranged judgment)

Table 1
Demographic variables and scores (SD) on the neuropsychological tasks for the three groups

	Healthy controls $n = 14$	MCI higher-cognition $n = 13$	MCI lower-cognition $n = 13$
Gender	8F/6M	8F/5M	7F/6M
Age	67.21 (6.80)	68.62 (10.30)	67.08 (6.29)
Education	14.57 (3.76)	15.31 (3.83)	13.62 (3.91)
MDRS	140.33 (2.65)	139.31 (2.81)	129.92 (4.48)[b]
MMSE	29.29 (1.14)	28.85 (1.57)	26.46 (1.56)[b]
SMAF		−0.83 (0.83)	−1.33 (1.13)
Boston Naming Test		13.92 (1.12)	12.46 (1.71)[c]
Coding (WAIS-III)	11.29 (2.30)	9.77 (2.65)	8.92 (2.69)
Benton Judgment of line orientation		24.85 (3.58)	22.62 (4.11)
Copy of Rey's Figure (time)		216.69 (105.64)	251.38 (144.08)
Copy of Rey's Figure (score)		31.35 (3.26)	30.08 (3.48)
Immediate recall of Rey's Figure (score)		12.46 (5.19)	8.27 (5.99)
Delayed recall of Rey's Figure (score)		13.81 (4.99)	7.34 (5.21)[d]
Stroop 3rd plate (time)		29.68 (6.78)	32.57 (8.56)
Stroop 3rd plate (errors)		0.92 (1.04)	1.54 (2.54)
RL/RI-16 3rd free recall	12.21 (2.32)	10.15 (2.54)	5.23 (2.59)[b,e]
RL/RI-16 delayed free recall	12.71 (2.40)	9.52 (3.86)[a]	4.85 (3.08)[b,e]

[a]impairment relative to controls at $p < 0.05$; [b]impairment relative to controls at $p < 0.001$; [c]impairment relative to MCI higher-cognition at $p < 0.05$; [d]impairment relative to MCI higher-cognition at $p < 0.01$; [e]impairment relative to MCI higher-cognition at $p < 0.001$.

Table 2
Scores (SD) on the behavioral task for the three groups

	Healthy controls $n = 14$	MCI higher-cognition $n = 13$	MCI lower-cognition $n = 13$
%correct (item recognition)	84.01 (18.92)	83.08 (10.79)	61.51 (11.58)[b,e]
%correct (associative recognition)	67.74 (14.49)	70.03 (15.36)	52.04 (7.93)[b,e]
Hit rate (item recognition)	0.84 (0.23)	0.78 (0.26)	0.64 (0.28)
False alarm (item recognition)	0.09 (0.12)	0.20 (0.22)	0.43 (0.23)[a]
d' (item recognition)	3.34 (1.47)	2.42 (1.09)	0.82 (0.87)[b,e]
Hit rate (associative recognition)	0.79 (0.21)	0.77 (0.25)	0.58 (0.31)
False alarm (associative recognition)	0.38 (0.21)	0.42 (0.29)	0.55 (0.36)
d' (associative recognition)	1.33 (0.77)	1.28 (1.39)	0.10 (0.97)[b,e]

[a]impairment relative to controls at $p < 0.05$; [b]impairment relative to controls at $p < 0.001$; [c]impairment relative to MCI higher-cognition at $p < 0.05$; [d]impairment relative to MCI higher-cognition at $p < 0.01$; [e]impairment relative to MCI higher-cognition at $p < 0.001$.

as a within-subject factor was computed using the mean percentage of correctly recognized pairs as a dependent variable. A Group effect ($F_{(2,37)} = 9.87$, $p < 0.001$) and a Condition effect ($F_{(1,37)} = 79.35$, $p < 0.001$) were observed. Tukey's post hoc test showed that healthy controls and persons in the MCI higher-cognition group recognized more word pairs than those in the MCI lower-cognition group ($p < 0.001$ for both groups), but that the healthy control and MCI higher-cognition groups did not differ from each other. In addition, the Condition effect was due to all three groups performing worse on the intact/rearranged judgment condition than on the old/new judgment condition. No Group-by-Condition interaction was found. Because both Group and Condition showed a significant effect on performance level, all fMRI analyses were computed using individual performance scores as a covariate. All analyses were also performed without the covariate. This resulted in a slight decrease in the amount of regions that showed significant activation. However, it did not change the general pattern of results.

Hit rates, false alarms and an index of sensitivity (d' = Z(hit rates) – Z(false alarms)) were also computed (Table 2). A two-way ANOVA with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (old/new judgment, intact/rearranged judgment) as a within-subject factor and d' as the dependent variable led to the same pattern of results as with the mean percentage of correctly recognized pairs.

fMRI data

Within-group comparisons

Item recognition. The areas of activation for the old/new judgment condition are presented in Table 3 and Fig. 2 for the three groups separately. In this condition, all groups showed activation in the left inferior and superior parietal lobules and the precuneus (BA 7, 39, and/or 40), the occipital lobe on both sides (BA 17, 18, and/or 19), the right medial prefrontal cortex and cingulate cortex (BA 8, 32) and the left Broca's area (BA 44). In addition to these common areas of activation, healthy controls showed activation in the right cerebellum and the left dorsolateral prefrontal cortex (BA 46). In the MCI higher-cognition group, the condition was associated with additional areas of activation in the right inferior parietal lobule (BA 39, 40), the left medial prefrontal and anterior cingulate cortex (BA 8, 24, and/or 32), the left premotor area (BA 6), the left precentral and postcentral gyri (BA 2, 3, and/or 4), the left ventrolateral prefrontal cortex (BA 45, 47), the right ventrolateral prefrontal cortex (44, 45, 47), and the right dorsolateral prefrontal cortex (BA 46). In addition to the common areas of activation mentioned above, the MCI lower-cognition group showed areas of activation in the right cerebellum, the inferior parietal lobule bilaterally (BA 39, 40), the medial prefrontal and anterior cingulate cortex bilaterally (BA 8, 24, and/or 32), the premotor area bilaterally (BA 6), the left precentral and postcentral gyri (BA 2, 3, and/or 4), the ventrolateral prefrontal cortex bilaterally (BA 44, 45, 47) and the left dorsolateral prefrontal cortex (BA 46).

Associative recognition. The areas of activation for the intact/rearranged judgment condition are presented in Table 4 and Fig. 2 for the three groups separately. This condition was associated with activation in the left occipital lobe (BA 17, 18, and/or 19) and the right medial prefrontal cortex and cingulate cortex (BA 8, 32) in all three groups. Healthy controls also showed areas of activation in the left and right inferior and superior parietal lobules and the precuneus (BA 7, 39,

Table 3
Clusters (>10 voxels) significantly more activated during the recognition of old/new word pairs condition than during the visual fixation condition for Healthy controls, MCI higher-cognition, and MCI lower-cognition, with cluster size, peak voxel MNI coordinates, and corresponding *t*-values

Activated areas (Brodmann area) ($p < 0.05$, corrected)	Cluster size	*x*	*y*	*z*	*t*-value
Healthy controls: Recognition old/new > visual fixation					
Left occipital lobe (17, 18, 19)	193	−30	−75	−18	10.01
Right occipital lobe (17, 18)	117	15	−87	−3	8.63
Left inferior and superior parietal lobules and precuneus (7, 39, 40)	49	−30	−66	39	6.87
Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	45	6	15	51	6.77
Right cerebellum	59	21	−54	−21	6.36
Left prefrontal cortex (44, 46)	15	−45	18	30	5.49
MCI higher-cognition: Recognition old/new > visual fixation					
Left occipital lobe (18, 19)	128	−30	−75	−18	10.58
Left/Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	90	6	21	42	8.28
Left inferior and superior parietal lobules and precuneus (7, 39)	90	−27	−63	42	7.66
Right inferior and superior parietal lobules and precuneus (7, 39, 40)	81	33	−66	45	7.19
Right dorsolateral prefrontal cortex (46)	42	45	27	27	7.15
Right occipital lobe (17)	43	18	−90	−3	6.84
Right prefrontal cortex (6, 44, 45, 47)	33	33	27	0	6.69
Left prefrontal cortex (6, 44, 45, 47)	47	−39	0	33	5.98
Left precentral and postcentral gyri (3, 4)	17	−36	−30	54	5.71
MCI lower-cognition: Recognition old/new > visual fixation					
Left occipital lobe (17, 18, 19)	314	−18	−90	−9	10.14
Right occipital lobe (17, 18)	153	18	−90	−6	9.42
Left/Right superior and medial prefrontal cortex and anterior cingulate cortex (6, 8, 24, 32)	252	6	24	42	8.55
Left precentral and postcentral gyri and left inferior parietal lobule (2, 3, 4, 39, 40)	179	−36	−60	39	7.10
Left dorsolateral prefrontal cortex (46)	35	−42	24	27	7.02
Left prefrontal cortex (6, 44, 45)	70	−45	6	36	6.91
Right cerebellum	59	21	−54	−21	6.69
Right inferior parietal lobule (39, 40)	36	33	−63	36	6.44
Left ventrolateral prefrontal cortex (47)	21	−33	24	0	5.99
Right cerebellum	10	3	−63	−21	5.73
Right ventrolateral prefrontal cortex (44, 45, 47)	17	36	24	3	5.65

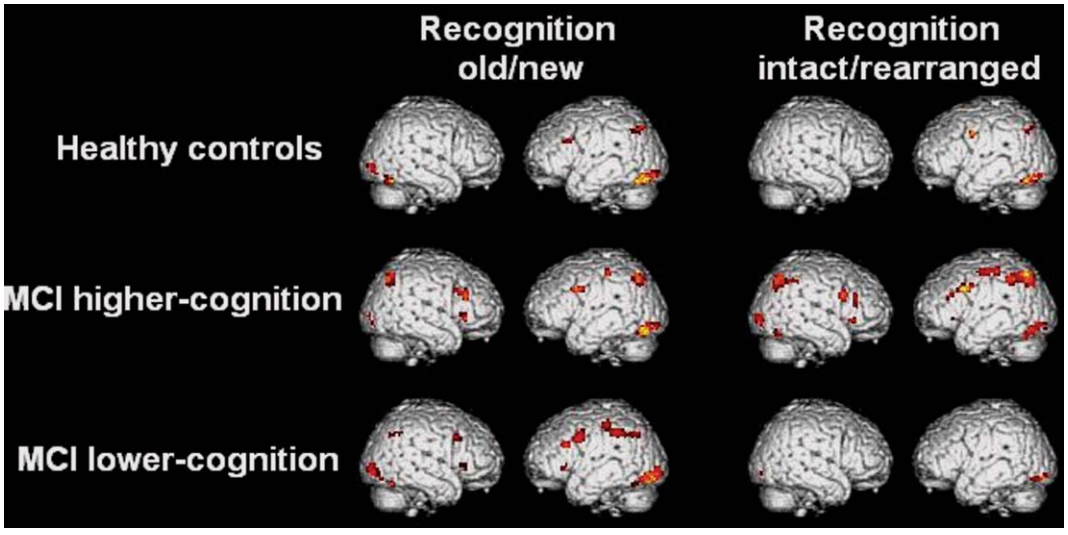

Fig. 2. Cerebral activations ($p < 0.05$, FWE corrected, cluster size >5 voxels) on the recognition of old/new word pairs condition and on the recognition of intact/rearranged word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups.

and/or 40), the left Broca's area (BA 44), the left premotor area (BA 6), and the left medial prefrontal cortex and cingulate cortex (BA 8, 32). The MCI higher-cognition group also showed areas of activation in the left and right inferior and superior parietal lobules and the precuneus (BA 7, 39, and/or 40), the left Broca's

Table 4
Clusters (>10 voxels) significantly more activated during the encoding of intact/rearranged word pairs condition than during the visual fixation condition for Healthy controls, MCI higher-cognition, and MCI lower-cognition, with cluster size, peak voxel MNI coordinates, and corresponding *t*-values

Activated areas (Brodmann area) ($p < 0.05$, corrected)	Cluster size	*x*	*y*	*z*	*t*-value
Healthy controls: Recognition intact/rearranged > visual fixation					
Left occipital lobe (18, 19) and left cerebellum	87	−30	−75	−18	8.13
Left/Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	84	6	15	48	7.30
Left prefrontal cortex (6, 44)	18	−45	0	36	6.49
Left inferior and superior parietal lobules and precuneus (7, 39)	19	−30	−66	39	6.11
MCI higher-cognition: Recognition intact/rearranged > visual fixation					
Left inferior and superior parietal lobules and precuneus (7, 39, 40)	215	−27	−63	45	8.27
Right inferior and superior parietal lobules and precuneus (7, 39, 40)	133	33	−66	42	7.76
Left occipital lobe (17, 18, 19)	96	−27	−75	−15	7.68
Right occipital lobe (17, 18)	68	18	−90	−3	7.39
Left prefrontal cortex (6, 9, 44)	73	−42	12	33	7.32
Right medial prefrontal cortex, premotor area and anterior cingulate cortex (6, 8, 32)	44	6	21	42	7.01
Right dorsolateral prefrontal cortex (9, 46)	39	48	15	27	6.78
Left dorsolateral prefrontal cortex (46)	11	−45	27	24	6.48
Right ventrolateral prefrontal cortex (44, 45, 47)	20	33	27	−3	6.26
Right cerebellum	22	21	−54	−21	6.18
Left precentral and postcentral gyri and premotor area (3, 4, 6)	59	−39	−15	54	6.11
Left ventrolateral prefrontal cortex (45, 47)	17	−30	21	6	5.95
Right occipital lobe (19)	13	39	−66	−21	5.81
Right dorsolateral prefrontal cortex (46)	20	42	30	12	5.73
MCI lower-cognition: Recognition intact/rearranged > visual fixation					
Left occipital lobe (18)	56	−15	−87	−9	6.84
Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	31	6	30	39	6.17
Right occipital lobe (17)	15	15	−87	−6	5.90

area (BA 44), the left premotor area (BA 6), the left and right dorsolateral prefrontal cortices (BA 9, 46), the right ventrolateral prefrontal cortex (BA 44, 45, 47), the left ventrolateral prefrontal cortex (BA 45, 47), the left motor postcentral and precentral gyri (BA 3, 4), and the right cerebellum. The MCI lower-cognition group did not recruit additional regions during this condition.

Between-group comparisons

Between-group comparisons were performed to directly compare the differences in activation as a function of the recognition condition between the two MCI groups and the healthy control group. The data is reported in Table 5 and Fig. 3.

MCI higher-cognition versus healthy controls. In the intact/rearranged condition (associative recognition), analyses indicated a number of brain areas with more activation in persons in the MCI higher-cognition group than in healthy controls. More activation was found in the left inferior parietal lobule (BA 40), the right temporal lobe (BA 37, 41), the left and right dorsolateral prefrontal cortices (BA 9), and the right ventrolateral prefrontal cortex (BA 44). During the old/new condition (item recognition), no area showed significantly more activation in the MCI higher-cognition group than in healthy controls. The only significant differences associated with item-recognition between these two groups were found in the right posterior cingulate cortex and parahippocampal gyrus, where more activation was found in healthy controls than in persons in the MCI higher-cognition group. Areas of hyperactivation were thus found exclusively for associative recognition in MCI higher-cognition.

MCI lower-cognition versus healthy controls. In the intact/rearranged condition (associative recognition), no areas showed more activation in the MCI lower-cognition group than in healthy controls. By contrast, the old/new condition (item recognition) was associated with more activation in MCI lower-cognition than in healthy controls in many areas including the left dorsolateral prefrontal cortex (BA 46), the medial prefrontal cortex bilaterally (BA 8), the left inferior parietal lobule (BA 40), and the anterior cingulate cortex bilaterally (BA 24, 32). Areas of hyperactivation were thus found exclusively for item recognition in the MCI lower-cognition group.

MCI higher-cognition versus MCI lower-cognition. The only significant difference of activation between

Table 5
Clusters (>5 voxels) significantly more activated in Healthy controls than in MCI higher- and MCI lower-cognition or significantly more activated in MCI higher- and MCI lower-cognition than in Healthy controls, with cluster size, peak voxel MNI coordinates, and corresponding *t*-values

Activated areas (Brodmann area) ($p < 0.001$, uncorrected)	Cluster size	*x*	*y*	*z*	*t*-value
MCI higher-cognition > Healthy controls: Recognition intact/rearranged					
Right dorsolateral prefrontal cortex (9)	19	3	42	48	4.21
Left inferior parietal lobule (40)	12	−48	−45	48	3.90
Right lateral temporal lobe (37)	13	51	−57	−3	3.74
Right lateral temporal lobe (41)	6	42	−21	12	3.74
Left dorsolateral prefrontal cortex (9)	6	−45	15	42	3.61
Right ventrolateral prefrontal cortex (44)	6	48	12	24	3.58
Healthy controls > MCI higher-cognition: Recognition intact/rearranged					
None					
MCI higher-cognition > Healthy controls: Recognition old/new					
None					
Healthy controls > MCI higher-cognition: Recognition old/new					
Right cingulate cortex and parahippocampal gyrus	25	6	−42	3	4.09
MCI lower-cognition > Healthy controls: Recognition intact/rearranged					
None					
Healthy controls > MCI lower-cognition: Recognition intact/rearranged					
None					
MCI lower-cognition > Healthy controls: Recognition old/new					
Left dorsolateral prefrontal cortex (46)	22	−27	48	21	4.25
Left/Right medial prefrontal cortex (8)	20	0	36	51	4.10
Left inferior parietal lobule (40)	6	−48	−51	39	3.52
Left/Right anterior cingulate cortex (24, 32)	8	6	33	6	3.51
Healthy controls > MCI higher-cognition: Recognition old/new					
None					
MCI higher-cognition > MCI lower-cognition: Recognition intact/rearranged					
Right precuneus and superior parietal lobule (7)	28	24	−69	51	3.77
Left precuneus and superior parietal lobule (7)	12	−24	−66	51	3.71
MCI lower-cognition > MCI higher-cognition: Recognition intact/rearranged					
None					
MCI higher-cognition > MCI lower-cognition: Recognition old/new					
None					
MCI lower-cognition > MCI higher-cognition: Recognition old/new					
None					

the two MCI groups was observed in the precuneus and superior parietal lobule (BA 7) bilaterally where MCI higher-cognition had more activation than MCI lower-cognition during the intact/rearranged condition. No other differences were found.

Between-task comparison

Between-task comparisons were performed in healthy controls to highlight the regions that are specifically more activated by each task. The data is reported in Table 6. Healthy controls showed more activation during the old/new condition than in the intact/rearranged condition in the medial prefrontal cortex bilaterally (BA 10), in the parahippocampal gyri bilaterally, and in the right middle and superior temporal gyrus (BA 19, 39). In contrast, they showed more activation during the intact/rearranged condition than in the old/new condition in the left basal ganglia and in the right anterior cingulate cortex (BA 24).

DISCUSSION

This paper assessed the effect of disease severity on the dynamics of compensatory brain plasticity in individuals with MCI. Scores on the MDRS reflected the degree of participants' global cognitive functioning, whereas an old/new judgment and an intact/rearranged judgment measured item and associative recognition, respectively. Our model predicts that disease severity would have a different effect on brain activation depending on the cognitive process measured: Individuals with less severe MCI were expected to show

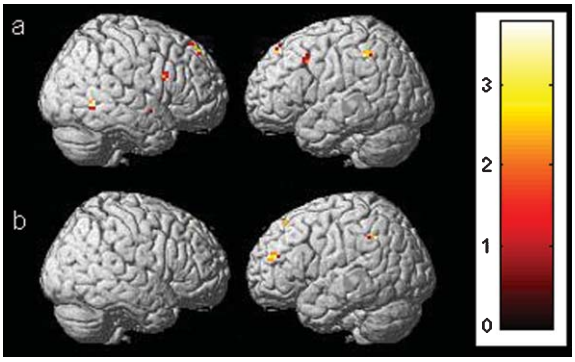

Fig. 3. Group differences in cerebral activations ($p < 0.001$, uncorrected, cluster size > 5 voxels) for (a) areas showing significantly more activation in the MCI higher-cognition group than in Healthy controls for the recognition intact/rearranged task and (b) areas showing significantly more activation in the MCI lower-cognition group than in Healthy controls for the recognition old/new task.

neural compensation for associative recognition only, whereas those with more severe MCI were expected to show neural compensation for item recognition only. This was hypothesized because recollection is impaired earlier than familiarity in the MCI-to-AD continuum [19, 20, 52]. As recollection plays a significant role in associative recognition tasks whereas familiarity-based processes are sufficient to support item recognition [16, 17], this study compared brain activation associated with either tasks.

Overall, results support our hypotheses (Fig. 3); MCI persons in a milder stage recruit additional brain areas, compared to healthy controls, during associative recognition while showing fairly similar brain activations during item recognition. The pattern is strikingly different in MCI individuals at a later stage of the disease: we found no hyperactivation for associative recognition, but a network of hyperactivated brain areas during item recognition. Therefore, persons with MCI would experience a shift in hyperactivation (see Fig. 1) from associative to item recognition as a function of their progress in disease severity, indicating a compensation breakdown for associative recognition and an emergence of compensatory mechanisms for item recognition. This shift in hyperactivation is in agreement with the neurodegenerative fMRI model proposed by Prvulovic and collaborators [8] and with recent data that show a similar compensation breakdown in individuals with late MCI for the encoding of information [53].

As predicted, many of the regions that showed hyperactivation were located in brain regions that have been involved with the retrieval mode (i.e., the dorsolateral and ventrolateral prefrontal cortices [27]). This larger recruitment in regions specialized in the retrieval mode probably reflects the fact that brain regions affected by the disease need to increase their activation to optimize performance. However, we also observed additional activations in regions that are usually not reported as being involved in either verbal episodic tasks or in the retrieval mode (i.e., the right temporal lobe, the precuneus and the inferior and superior parietal lobules). These new activations may represent the recruitment of additional compensatory networks. This is also reflected by the direct comparison between the two MCI subgroups. This comparison revealed that MCI higher-cognition show more activation in posterior regions than MCI lower-cognition during associative recognition.

Another finding relates to more bilateral activation of the prefrontal cortex in both MCI groups than in healthy controls. MCI higher-cognition showed bilateral activation of many prefrontal regions during both the old/new condition (BA 6, 44, 45, 47) and the intact/rearranged condition (BA 9, 44, 46), whereas the MCI lower-cognition showed bilateral activation during the old/new condition only (BA 44, 45, 47). This bilateral activation is in agreement with recent models that highlight the importance of interhemispheric

Table 6
Clusters (>10 voxels) significantly more activated during the recognition of old/new word pairs condition than during the recognition intact/rearranged word pairs or during the recognition of intact/rearranged word pairs condition than during the recognition old/new word pairs for Healthy controls, with cluster size, peak voxel MNI coordinates, and corresponding *t*-values

Activated areas (Brodmann area) ($p < 0.005$, uncorrected)	Cluster size	*x*	*y*	*z*	*t*-value
Healthy controls: Recognition old/new > Recognition intact/rearranged					
Left/Right medial prefrontal cortex (10)	26	−3	66	3	3.30
Left parahippocampal gyrus	7	−12	−39	3	3.18
Right parahippocampal gyrus	9	24	−30	−15	3.17
Right middle and superior temporal gyrus (19, 39)	10	48	−63	15	2.99
Healthy controls: Recognition intact/rearranged > Recognition old/new					
Left basal ganglia	21	−6	3	−3	3.37
Right anterior cingulated cortex (24)	11	6	36	3	2.96

interaction in neural compensatory mechanisms [9, 10]. Similarly, the left inferior parietal lobule (BA 40) appears to be a key component of the compensatory network used during MCI, as it showed hyperactivation in the MCI higher-cognition group during the intact/rearranged condition and in the MCI lower-cognition group during the old/new condition. The involvement of the left lateral parietal lobe in memory retrieval is in line with data reported in previous studies (for review, see [54]) and is often interpreted as reflecting attentional processes directed at internal mnemonic representations. Thus, it is plausible that one of the compensatory mechanisms used by individuals with MCI involves allocating increased attentional resources to the memory task.

It must be noted that our fMRI analyses were covaried for performance level since the performances of the MCI lower-cognition group were lower than the ones of the two other groups. This was done to assess whether the group differences in brain activation was due to the fact that participants found themselves at different points on the difficulty continuum. This is important as some studies have suggested that easy tasks would yield less activation than difficult ones [8]. Thus groups that show performance differences might show different brain activations because they require different brain resources to complete the task. This is a relevant question here, as it has been shown that performance level explains a large part of the differences in brain activation between healthy controls and patients with AD [55]. In our case, there were group differences on some of the task but covarying for performance did not change the pattern of activation differences. It is thus fair to conclude that activation differences cannot be amenable to mere differences in task difficulty or degrees of effort put on the task. Importantly, a similar pattern of results was found when repeating our analyses without covarying for performance, suggesting that our findings reflect an intrinsic difference in the neural networks of our participants rather than a simple effect of performances on brain activation.

Behavioral results indicate impaired associative recognition and item recognition in persons in the MCI-lower cognition group, but preserved performance in those in the MCI higher-cognition group. Although many studies have found intact item or familiarity-based recognition in MCI [21–23, 52], the contrary has been observed in one study [24]. Our results point to a possible explanation for the divergent findings in the literature. The different levels of severity in the MCI groups may explain the different levels of impairment on the associative and item recognition tasks. It may also appear surprising that the MCI higher-cognition group performed at the same level as the healthy controls on the experimental tasks even though they met criteria for MCI and were thus impaired on the more classical neuropsychological tests such as the free and cued word recall task and text memory task. This can probably be explained by the fact that the clinical neuropsychological evaluation of memory relied on free recall, whereas that of experimental tasks used recognition. The current literature is rather controversial regarding this issue, but some studies have reported a preservation of recognition memory in MCI [56–59]. Another possible explanation is disease severity, as those studies reporting preserved recognition relied on MCI participants who were slightly less impaired (mean MMSE of 27.5 and 27.0, respectively) than those reporting impaired recognition (mean MMSE of 26.1 and 26.4, respectively). Accordingly, in this study, individuals with less severe MCI (mean MMSE of 28.85) showed preserved recognition, whereas those with more severe MCI (mean MMSE of 26.46) showed impaired recognition.

The present study does have some limitations. First, the design was cross-sectional and therefore did not directly measure the MCI-to-AD continuum. A related limitation concerns the possibility that some of the individuals with MCI were not in a prodromal phase of AD. Note, however, that 58% of the individuals with MCI in our study either showed cognitive decline or progressed to AD after only two years, suggesting that a large proportion of those participants may be on a pathological pathway. A third potential limitation is our use of a block fMRI design rather than an event-related design. One characteristic of the block design is that it measures blood flow over a relatively large temporal frame as opposed to an event-related design. In the case of memory retrieval tasks, it has been proposed that this type of design is more sensitive to the regions involved in the retrieval mode (e.g., prefrontal regions, [27]). This has important implications for the interpretation of the data and may explain the predominance of prefrontal, over hippocampal, activations in this study, as hippocampal activations have been more commonly observed in event-related designs where successful retrieved items are compared to unsuccessful retrieved items [60]. Interestingly, both MCI groups tended to activate their prefrontal cortex more bilaterally than the healthy control group, which may suggest that they need additional resources for their retrieval modes. Relatedly, it must be mentioned that block design does not allow a comparison between correct and incorrect

responses and hence cannot reflect the neural correlates of successful encoding and retrieval. However, this design is suitable for patients with memory difficulties as the conditions alternate less frequently, and it offers maximal detection power [46]. The power issue was particularly critical in our context, as we were looking for differences related to severity levels likely to yield more modest effect sizes than when comparing a clinical with a control group. Also, the use of a clinical measure (i.e., MDRS) as an indicator of disease severity may not be ideal. We favored a measure of global cognitive performance because it is closer to the current criteria for identifying MCI and AD than are neuroanatomical markers. It is noteworthy that the MDRS scores for individuals with MCI correlated strongly with their performances on the RL/RI-16 3rd free recall ($r = 0.68$, $p < 0.001$) and delayed free recall ($r = 0.71$, $p < 0.001$) tasks. This supports our contention that using this score as a measure of disease severity is sound. Finally, the fact that the MCI lower-cognition group showed a level of performances close to chance level during the associative recognition task might have influenced some of the brain activation results. Indeed, this may indicate that some individuals of this group were not able to fully engage the cognitive processes required to successfully complete the task. However, this study was mainly interested in the retrieval mode, which may very well be activated even if the performances of the subjects are at chance level, and it is therefore less likely that our results were confounded by this floor effect. Along that line, we are comforted by the fact that our activations are coherent with the retrieval mode rather than with successful retrieval.

Overall, the findings of this study point toward the presence of neural compensation and brain plasticity throughout the entire phase of MCI. However, this phase does feature a change in the pattern of neural compensation (Fig. 3). At first, persons with MCI recruit a large network of additional brain areas during associative recognition, and this is accompanied by a normal performance level. During this early phase, item recognition is unimpaired behaviorally and is associated with fairly similar brain activation as that found in healthy controls. As individuals with MCI progress in the disease, they experience a shift in their pattern of neural compensation: the neural and behavior compensation, found with associative recognition, breaks down and makes way for compensation during item recognition. This pattern of compensation emergence and breakdown during the MCI phase indicates that brain plasticity relies on complex and dynamic processes that are determined as much by the extent and nature of brain lesions as by the particular type of cognitive processes upon which brain plasticity is measured.

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REFERENCES

[1] Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J (2002) Natural history of mild cognitive impairment in older persons. *Neurology* **59**, 198-205.

[2] Grady CL (2008) Cognitive neuroscience of aging. *Ann N Y Acad Sci* **1124**, 127-144.

[3] Rajah MN, D'Esposito M (2005) Region-specific changes in prefrontal function with age: A review of PET and fMRI studies on working and episodic memory. *Brain* **128**, 1964-1983.

[4] Friston KJ, Price CJ (2003) Degeneracy and redundancy in cognitive anatomy. *Trends Cogn Sci* **7**, 151-152.

[5] Price CJ, Friston KJ (2002) Degeneracy and cognitive anatomy. *Trends Cogn Sci* **6**, 416-421.

[6] Rapoport SI, Grady CL (1993) Parametric *in vivo* brain imaging during activation to examine pathological mechanisms of functional failure in Alzheimer disease. *Int J Neurosci* **70**, 39-56.

[7] Wermke M, Sorg C, Wohlschlager AM, Drzezga A (2008) A new integrative model of cerebral activation, deactivation and default mode function in Alzheimer's disease. *Eur J Nucl Med Mol Imaging* **35**(Suppl 1), S12-S24.

[8] Prvulovic D, Van de Ven V, Sack AT, Maurer K, Linden DE (2005) Functional activation imaging in aging and dementia. *Psychiatry Res* **140**, 97-113.

[9] Banich MT (1998) The missing link: The role of interhemispheric interaction in attentional processing. *Brain Cogn* **36**, 128-157.

[10] Cabeza R (2002) Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychol Aging* **17**, 85-100.

[11] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[12] Perri R, S0erra L, Carlesimo GA, Caltagirone C (2007) Amnestic mild cognitive impairment: Difference of memory profile in subjects who converted or did not convert to Alzheimer's disease. *Neuropsychology* **21**, 549-558.

[13] Clement F, Belleville S, Gauthier S (2008) Cognitive complaint in mild cognitive impairment and Alzheimer's disease. *J Int Neuropsychol Soc* **14**, 222-232.

[14] Cabeza R, Nyberg L (2000) Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* **12**, 1-47.

[15] Yonelinas AP, Aly M, Wang WC, Koen JD (2010) Recollection and familiarity: Examining controversial assumptions and new directions. *Hippocampus* **20**, 1178-1194.

[16] Yonelinas AP (1997) Recognition memory ROCs for item and associative information: The contribution of recollection and familiarity. *Mem Cognit* **25**, 747-763.

[17] Hockley WE, Consoli A (1999) Familiarity and recollection in item and associative recognition. *Mem Cognit* **27**, 657-664.

[18] Yonelinas AP, Otten LJ, Shaw KN, Rugg MD (2005) Separating the brain regions involved in recollection and familiarity in recognition memory. *J Neurosci* **25**, 3002-3008.

[19] Dalla Barba G (1997) Recognition memory and recollective experience in Alzheimer's disease. *Memory* **5**, 657-672.

[20] Gallo DA, Sullivan AL, Daffner KR, Schacter DL, Budson AE (2004) Associative recognition in Alzheimer's disease: Evidence for impaired recall-to-reject. *Neuropsychology* **18**, 556-563.

[21] Westerberg CE, Paller KA, Weintraub S, Mesulam MM, Holdstock JS, Mayes AR, Reber PJ (2006) When memory does not fail: Familiarity-based recognition in mild cognitive impairment and Alzheimer's disease. *Neuropsychology* **20**, 193-205.

[22] Anderson ND, Ebert PL, Jennings JM, Grady CL, Cabeza R, Graham SJ (2008) Recollection- and familiarity-based memory in healthy aging and amnestic mild cognitive impairment. *Neuropsychology* **22**, 177-187.

[23] Hudon C, Belleville S, Gauthier S (2009) The assessment of recognition memory using the Remember/Know procedure in amnestic mild cognitive impairment and probable Alzheimer's disease. *Brain Cogn* **70**, 171-179.

[24] Wolk DA, Signoff ED, Dekosky ST (2008) Recollection and familiarity in amnestic mild cognitive impairment: A global decline in recognition memory. *Neuropsychologia* **46**, 1965-1978.

[25] Wheeler MA, Stuss DT, Tulving E (1997) Toward a theory of episodic memory: The frontal lobes and autonoetic consciousness. *Psychol Bull* **121**, 331-354.

[26] Velanova K, Jacoby LL, Wheeler ME, McAvoy MP, Petersen SE, Buckner RL (2003) Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J Neurosci* **23**, 8460-8470.

[27] Buckner RL (2003) Functional-anatomic correlates of control processes in memory. *J Neurosci* **23**, 3999-4004.

[28] Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002) Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage* **17**, 1394-1402.

[29] Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, Kim JS, Alvarado M, Kramer AF (2007) Training-induced functional activation changes in dual-task processing: An FMRI study. *Cereb Cortex* **17**, 192-204.

[30] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[31] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC (2004) Mild cognitive impairment–beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240-246.

[32] Buschke H (1984) Cued recall in amnesia. *J Clin Neuropsychol* **6**, 433-440.

[33] Van der Linden M, Adam S, Agniel A, Baisset-Mouly C, Bardet F, Coyette F, Desgranges B, Deweer B, Ergis AM, Gély-Nargeot MC, Grimomprez L, Juillerat AC, Kalafat M, Poitrenaud J, Sellal F, Thomas-Antérion C (2004) *L'évaluation de troubles de la mémoire: Présentation de quatre tests de mémoire épisodique (avec étalonnage)*, Solal, Marseille.

[34] Signoret JL (1991) *Batterie d'efficience mnésique BEM 144*, Elsevier, Paris.

[35] Rey A (1959) *Test de copie d'une figure complexe: Manuel*, Les éditions du centre de psychologie appliquée, Paris.

[36] Regard M (1981) Cognitive rigidity and flexibility: A neuropsychological study. Unpublished Ph.D. dissertation, University of Victoria, Canada.

[37] Benton AL, Hamsher K, Varney NR, Spreen O (1983) *Contributions to neuropsychological assessment*, Oxford University Press, New York.

[38] Wechsler D (1997) *Wechsler Adult Intelligence Scale-III*, Psychological Corporation, New York.

[39] Kaplan EF, Goodglass H, Weintraub S (1983) *The Boston Naming Test (2nd edition)*, Lea & Febiger, Philadelphia, PA.

[40] Mattis S (1976) Mental status examination for organic mental syndrome in the elderly patient In *Geriatric Psychiatry*, Bellak L, Karasu TB, eds. Grune & Stratton, New York, pp. 77-121.

[41] Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* **12**, 189-198.

[42] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[43] American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* American Psychiatric Publishing, Inc.

[44] Freibergs V (1968) *Normes d'association libre aux 100 mots Kent-Rosanoff*.

[45] Freibergs V (1970) *Normes d'association libre aux premières cinq réponses des hiérarchies d'associations aux 100 mots Kent-Rosanoff*.

[46] Liu TT (2004) Efficiency, power, and entropy in event-related fMRI with multiple trial types Part II: Design of experiments. *Neuroimage* **21**, 401-413.

[47] Clement F, Belleville S (2010) Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biol Psychiatry* **68**, 894-902.

[48] Kircher T, Weis S, Freymann K, Erb M, Jessen F, Grodd W, Heun R, Leube DT (2007) Hippocampal activation in MCI patients is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry* **78**, 812-818.

[49] Sole-Padulles C, Bartres-Faz D, Junque C, Vendrell P, Rami L, Clemente IC, Bosch B, Villar A, Bargallo N, Jurado MA, Barrios M, Molinuevo JL (2009) Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **30**, 1114-1124.

[50] Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, Grodd W (2007) Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging* **28**, 404-413.

[51] Ries ML, Schmitz TW, Kawahara TN, Torgerson BM, Trivedi MA, Johnson SC (2005) Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage* **29**, 485-492.

[52] Belleville S, Menard MC, Lepage E (2011) Impact of novelty and type of material on recognition in healthy older adults and persons with mild cognitive impairment. *Neuropsychologia* **49**, 2856-2865.

[53] Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, DePeau K, Rentz DM, Selkoe DJ, Blacker D, Albert MS, Sperling RA (2006) Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: An independent component analysis. *J Neurosci* **26**, 10222-10231.

[54] Wagner AD, Shannon BJ, Kahn I, Buckner RL (2005) Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci* **9**, 445-453.

[55] Gould RL, Brown RG, Owen AM, Bullmore ET, Williams SC, Howard RJ (2005) Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *Am J Psychiatry* **162**, 2049-2060.

[56] Perri R, Carlesimo GA, Serra L, Caltagirone C (2005) Characterization of memory profile in subjects with amnestic mild cognitive impairment. *J Clin Exp Neuropsychol* **27**, 1033-1055.

[57] Gronholm-Nyman P, Rinne JO, Laine M (2010) Learning and forgetting new names and objects in MCI and AD. *Neuropsychologia* **48**, 1079-1088.

[58] Seelye AM, Howieson DB, Wild KV, Moore MM, Kaye JA (2009) Wechsler Memory Scale-III Faces test performance in patients with mild cognitive impairment and mild Alzheimer's disease. *J Clin Exp Neuropsychol* **31**, 682-688.

[59] Dudas RB, Clague F, Thompson SA, Graham KS, Hodges JR (2005) Episodic and semantic memory in mild cognitive impairment. *Neuropsychologia* **43**, 1266-1276.

[60] Huijbers W, Pennartz CM, Rubin DC, Daselaar SM (2011) Imagery and retrieval of auditory and visual information: Neural correlates of successful and unsuccessful performance. *Neuropsychologia* **49**, 1730-1740.