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Altered brain activities associated with neural repetition effects in mild cognitive impairment patients

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Abstract

Older adults with mild cognitive impairment (MCI) manifest impaired explicit memory. However, studies on implicit memory such as repetition effects in persons with MCI have been limited. In the present study, 17 MCI patients and 16 healthy normal controls (NC) completed a modified delayed-match-to-sample task (DMST) while undergoing functional magnetic resonance imaging. We aim to examine the neural basis of repetition; specifically, to elucidate whether and how repetition-related brain responses are altered in participants with MCI. When repeatedly rejecting distracters, both NC and MCI showed similar behavioral repetition effects; however, in both whole-brain and region-of-interest analyses of functional data, persons with MCI showed reduced repetition-driven suppression in the middle occipital and middle frontal gyrus. Further, individual difference analysis found that activation in the left middle occipital gyrus was positively correlated with rejecting reaction time and negatively correlated with accuracy rate, suggesting it could predict repetition behavioral performance. These findings provide new evidence to support the view that neural mechanisms of repetition effect are altered in MCI, who manifest compensatory repetition-related brain activities along with their neuropathology.

Keywords

mild cognitive impairment; repetition; delayed-match-to-sample task; fMRI; repetition-driven suppression

1. Introduction

Memory impairment is one of the hallmarks of early Alzheimer's disease (AD). It is well established that their ability to encode and retain new episodic memories declines severely [1–4]. Mild cognitive impairment (MCI), a transitional stage between normal aging and clinical status of dementia [5, 6], is similarly characterized in part by explicit memory impairment [7–9]. However, unlike the relation of MCI to explicit memory, the effect of MCI on implicit memory is less clear.

Implicit memory, also called implicit learning, is the ability to improve task performance based on prior exposure to identical or related stimuli [10]. Increased efficiency of performance is demonstrated as decreased reaction time or increased accuracy during tasks. One well-studied type of implicit memory is repetition priming during tasks such as the word-stem completion, fragmented object identification, or category-exemplar production paradigms. Certain forms of repetition priming may be more or less sensitive to AD, depending on whether the priming task is biased towards conceptual or perceptual processes [11, 12]. Brain imaging data support these behavioral findings; AD patients show a graded deficit in the brain areas such as medial temporal lobe (MTL), which subserves explicit memory, while relatively preserved functions in neocortical areas such as primary visual cortex, which subserves perceptual priming [13–15]. The growing literature on implicit memory in aging and AD has also revealed contradictory results that implicit memory appears spared in some cases, but impaired in others. Meta-analyses showed that there was a small but significant reduction of repetition priming in normal aging [16] and a larger reduction of repetition priming in AD [17]. The impairment in repetition priming is associated with the presence of neuropathology and the risk for developing AD, it could be considered as a potential neuropsychological marker for the disease [15].

The behavioral performance and brain basis of implicit memory in MCI are less studied compared with normal aging and AD. Since MCI is a cohort with high risk of conversion to AD, clarifying how this stage differs from normal aging in the repetition effect is crucial to understanding the pathological process. One potential tool for clarifying the characteristics of this stage has been functional magnetic resonance imaging (fMRI). In typical adults, functional MRI studies have demonstrated a well-characterized reduction of blood-oxygen-level-dependent (BOLD) signals to repeatedly presented stimuli in the temporo-occipital regions [18–21]. However, this repetition suppression is scarcely studied in persons with MCI. The goal of the present study was to examine alteration of repetition effects in persons with MCI in a hybrid delayed-match-to-sample task (DMST). Neural mechanisms of repeated working memory retrieval during DMST have been examined in both young adults and healthy older adults by event-related-potential (ERP) and fMRI measures [18, 22, 23]. In this task, participants are asked to memorize the sample stimuli at the beginning of each trial and then to indicate whether or not serially presented objects match the sample stimuli. In order to exclude the explicit memory component of the paradigm, we focused the current investigation on the repetition effect of distracter stimuli (i.e., non-match items).

We hypothesized that participants with MCI would show behavioral repetition effects similar to that of normal aging older adults, given the more automatic nature of implicit learning. However, neurally, we hypothesized that MCI patients would show altered neural repetition effects given the implication of neural activity changes in the early course of dementia. Specifically, MCI patients would show reduced repetition suppression in the temporo-occipital regions subserving priming processes. Moreover, we assessed the association between the activations of temporo-occipital regions and repetition behavioral performance to further test this hypothesis.

2. Methods

2.1 Participants

Thirty-three older adults (60 years old or older) participated in the study, among whom were 17 MCI patients (MCIs) and 16 healthy normal control participants (NCs). The participants of current study were from a community-based screening data pool in Beijing (healthy older adults, $n = 865$; MCI, $n = 115$; Dementia, $n = 21$) [24–26]. Among these 115 MCI patients, 43 were from the communities near the Beijing MRI Center for Brain Research (within a half-hour bus ride), and 13 of whom were not able to participate in the MRI protocol due to metal elements in the body. Thus, the remaining 30 MCI patients were contacted, and 17 agreed to complete the study. NC participants were randomly contacted from the same communities as the MCI patients. None of the MCI patients were taking any specific medications for their cognitive condition during the period of the study. Each participant completed a battery of neuropsychological tests, clinical assessment, and neuroimaging examinations. Research assistants with psychological background administered the neuropsychological battery, and experienced psychiatrists performed the clinical diagnoses. Diagnosis of MCI was mainly based on the Clinical Dementia Rating (CDR), the Global Deterioration Scale (GDS), and the Activities of Daily Life (ADL), supplemented by the psychiatrists' clinical experiences, scores on the Montreal Cognitive Assessment (MoCA), the Mini-Mental Status Examination (MMSE), the Neuropsychiatric Inventory (NPI) and the Hachinski Ischemic Score (HIS). The detailed diagnostic criteria included: (1) subjective complaints of memory loss, preferably corroborated by an informant; (2) preservation of general cognitive function; (3) a global CDR score of 0.5; (4) level 2 or level 3 in the GDS; (5) intact activities of daily life (ADL); and (6) an absence of dementia. See Table 1 for participants' demographics and neuropsychological test results. In addition, structural MRI data showed that MCI patients in this study exhibited significant gray matter (GM) loss in the middle part of the medial frontal lobe and the lateral frontal and parietal lobes, relative to NC participants. The structural impairment patterns are similar to those reported in previous studies of persons with MCI [27, 28].

This study was approved by the research ethics committees of the Institute of Psychology, Chinese Academy of Science (H11036). Informed consent was obtained from each participant, and they received 100 Chinese dollars (ca. 16 USD) for participation in the study.

2.2 Materials and procedures

The hybrid delayed-match-to-sample task (DMST) consisted of 32 trials separated into 4 blocks of 8 trials, which is modified from the previous delayed match-to-sample paradigms [18, 22, 23]. Each trial of the task consisted of two sample objects with green borders presented side by side to be remembered (for 3500 ms). The sample targets were followed by test objects presented for 1000 ms each with variant jitters of 800/900/1000/1100/1200 ms. Each trial lasted approximately 30 s. Test objects were classified into two groups: matching targets and non-matching distracters. Each trial contained a pseudo-random and counter-balanced presentation of target and distracter objects. Target objects were presented one, two, three, or four times, and distracter objects were each presented one, two, three, or

four times making up a total of 12 (or 13) test objects per trial (Figure 1). Thus, of 192 distracter stimuli in total, 64 stimuli served as firstly presented distracters (D1), 64 stimuli served as secondly presented distracters (D2), 44 stimuli served as the thirdly presented distracters (D3), and 22 stimuli served as fourthly presented distracters (D4). Participants were asked to determine whether each of the subsequent test objects matched the sample objects. They were required to respond by pressing a button with their right/left thumb finger for each test object in the trial that matched the sample objects or by pressing another button with their other thumb finger for each test object that did not match the sample objects. The association between hand and matching was counterbalanced among participants. For the visual processing control, the scrambled versions (containing the same spatial frequencies in *Fournier* domain) of the actual objects images were used as a baseline. Each of the scrambled nonsense picture block contains five scrambled pictures, and each one presented for 2s. Participants were asked to press both buttons when they saw the scrambled pictures. The DMST memory trials and the scrambled picture blocks were presented alternatively.

2.3 Image acquisition

Subjects were scanned using a Siemens Trio 3.0 tesla scanner (Erlangen, Germany) at the Beijing MRI Center for Brain Research. For each participant, functional echo planar image data were collected using the following parameters: time repetition (TR) = 2000 ms, time echo (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 200×200 mm², 33 axial slices, thickness = 3.0 mm, gap = 0.6 mm, acquisition matrix = 64×64, and in-plane resolution = 3.125×3.125. High-resolution, three-dimensional T1-weighted structural images were acquired for each subject, with the following parameters: 176 slices, acquisition matrix = 256×256, voxel size = 1×1×1 mm³, TR = 1900 ms, TE = 2.2 ms, and flip angle = 9°.

2.4 Data analysis

2.4.1 Behavioral data analysis—To examine repetition effect regardless of the explicit memory components, we focused on the distracters (non-match objects) only. Behavioral effects were indexed using mean response time (RT) and response accuracy measured as percentage of correct rejection for distracters. The repetition effect was defined as the decreasing extent of reaction time along with increasing number of repetitions. In order to match the stimuli number of thirdly and fourthly presented distracters to the firstly presented distracters (D1) and secondly presented distracters (D2), the thirdly and fourthly presented distracter stimuli were combined together (D3&4) for the further analysis. In addition, to better understand participants' task performance, we analyzed the group differences on the total reaction time and precision (Pr) of this delayed-match-to-sample task, of which Pr was calculated as correct acceptance of targets minus false rejection of distracters.

2.4.2 Image preprocessing—Functional MRI data were preprocessed using the statistical parametric mapping program (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). Functional image data were corrected for intra-volume acquisition time differences between slices using sinc interpolation and were corrected for inter-volume geometrical displacement due to head motion using a six-parameter (rigid body) spatial transformation. Participants included in this study all had head motion of less than 3 mm in any direction. The data were then normalized into the Montreal Neurological Institute (MNI) standard space using an

optimum 12-parameter affine transformation and nonlinear deformations. The normalized volumes were resampled to a voxel size of $3 \times 3 \times 3 \text{ mm}^3$. Finally, the images were spatially smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel.

2.4.3 Neuroimaging analysis—Statistical analysis was first performed individually for each participant. Differences between stimulus conditions were examined using the general linear model, after which group analysis was performed on the contrast images derived from the single subject analysis. To control for the potential confounding effects of head movement, six motion parameters (three translation and three rotation parameters) were entered into the GLM as regressors of no interest. Three approaches were adopted in the group analysis to determine the influence of MCI on the repetition effect. First, to assess the activation/deactivation of the experimental conditions, one-sample *t*-tests were adopted between the distracters and the baseline (scrambled pictures). It was termed as activation if a greater BOLD signal change was observed for distracters in distracter vs. scrambled pictures contrast, otherwise termed as deactivation if a greater BOLD response was observed for baseline. We examined the activation and deactivation brain regions for each condition (D1 vs. baseline, D2 vs. baseline, D3&4 vs. baseline) in both groups. Second, to determine the differences between groups, a two-sample *t*-test was adopted. We examined the BOLD signal differences between groups in each condition contrast to observe the influence of MCI on the repetition effect in brain activations. In order to illustrate the group differences more clearly, we made activation masks and deactivation masks across groups based on D1 vs. baseline/D2 vs. baseline/D3&4 vs. baseline contrasts to observe the MCI effect on the activation regions and deactivation regions separately. Third, to further investigate whether repetition-associated brain activities were affected by MCI, a region of interest (ROI) analysis was applied. ROIs were defined as regions that showed significantly greater activation and deactivation for D1 vs. baseline across MCIs and NCs; empirically, these included the middle occipital lobe, middle/inferior frontal gyrus, anterior cingulate, precuneus, and middle temporal gyrus. Then, we extracted the beta weights of ROIs and observed their changes during repetition. To determine the potential group differences, the signal changes for each participant from these ROIs were extracted and averaged for each stimulus type, and a repeated measure model of ANOVA was used to determine the main and interaction effects. In addition, the correlations of signal changes of ROIs and behavioral performance were also calculated within one block. As the values of reaction time are normally distributed while the values of correct response rate are skewed distributed, the pearson correlation and spearman correlation were conducted accordingly.

Within-group fMRI analyses were examined at a threshold corrected for multiple comparisons (corrected by false-discovery-rate, FDR correction, $p < .05$), whereas between group fMRI analyses were threshold at $p < .005$, cluster size > 26 voxels, using AlphaSim correction as described in previous work [29, 30]. All coordinates are reported in MNI format.

2.4.4 Structural image analysis—The loss of gray matter (GM) in MCI may have potential effects on the functional results. In the current study, a voxel-based morphometry (VBM) analysis was performed for structural images using DPABI (<http://rfmri.org/dpabi>).

Structural images of each participant were co-registered to mean functional images after motion correction using a linear transformation, and then segmented into GM, white matter, and cerebrospinal fluid in the MNI space [31]. Then, we performed a voxel-based 2-sample *t*-test on GM intensity maps to determine the pattern of GM atrophy in MCI patients. The statistical threshold was using the AlphaSim correction for multiple comparisons with a threshold of $p < 0.01$ at voxel level and a minimum cluster size of 1492 voxels.

3. Results

3.1 Behavioral results

Response time (RT) revealed main effects of repetition ($F(2, 62) = 41.52, p < .001$), shown as decreased RT with repetition that the RT of D3&4 was shorter than D1 ($p < .001$) and D2 ($p < .001$). The group difference was significant, shown as the averaged RT of MCIs was longer than that of NCs ($F(1, 31) = 9.66, p < .010$). However, the interaction between repetition and group was not significant ($F(2, 62) = 0.23, p = .799$) (Figure 2a). Concerning accuracy rate, there was a significant main effect of repetition ($F(2, 62) = 12.89, p < .001$), shown as the accuracy of D1 was higher than D2 ($p < .001$) and D3&4 ($p < .010$). The group difference was significant, shown as the accuracy of MCIs was lower than NCs ($F(1, 31) = 7.86, p < .010$). Also, there was no interaction between repetition and group ($F(2, 62) = 0.87, p = .424$) on accuracy rate (Figure 2b). Moreover, MCIs had lower Pr ($t = 2.75, df = 31, p < .010$; Figure 2d) and longer RT ($t = -3.29, df = 31, p < .010$; Figure 2c) than NCs overall in the delayed-match-to-sample task.

3.2 Neuroimaging results

3.2.1 Whole-brain analysis—A whole-brain analysis revealed widespread neural activity for distracter vs. baseline contrasts. Generally, both NCs and MCIs displayed activation (i.e., distracter > baseline) in the occipital cortex and the left middle frontal gyrus (Figure 3, Red). Moreover, both groups displayed deactivation (i.e., distracter < baseline) in the medial frontal gyrus, the middle temporal gyrus, and the inferior parietal lobule (Figure 3, Blue). Specifically, along with the repetition, NC group exhibited reliable activations in the middle occipital gyrus (MOG), fusiform, inferior frontal gyrus and middle frontal gyrus; and deactivations in inferior/medial frontal gyrus, superior temporal gyrus, and inferior parietal lobule (IPL; Figure 3, NC; supplementary Table S1 for details). The MCI group had significant clusters of activations in the MOG, superior parietal lobule, and middle/medial frontal gyrus; and deactivations in medial/inferior frontal gyrus (IFG), superior temporal gyrus, IPL, and posterior cingulate gyrus (Figure 3, MCI; supplementary Table S2 for details).

Group difference analyses were performed separately under the activation and deactivation mask in each presentation contrast to highlight those areas with relative reserving in MCI relative to those areas that were differentially affected. In D1 and D2, the NC and MCI group did not have significant activation and deactivation differences. However, in D3&4, MCI showed more activation than NC in the bilateral MOG, IPL, and medial frontal gyrus (Figure 4; supplemental Table S3 for details).

3.2.2 ROI analysis—ROI analysis in the MOG, middle/inferior frontal gyrus, anterior cingulate, precuneus, and middle temporal gyrus confirmed and extended the findings described above. Regarding with the activations, the repetition (D1 vs. D2 vs. D3&4) $\times$ group (NC vs. MCI) interaction was significant in the MOG ($F(2, 62) = 4.18, p < .05$) and middle frontal areas ($F(2, 62) = 4.90, p < .05$). The repetition-associated activations in the MOG were decreasing during repetitions in the NC group ($F(2, 30) = 5.56, p < .01$), while the activations first decreased in D2 but increased to the similar extent in D3&4 compared with D1 in the MCI group ($F(2, 32) = 3.76, p < .05$; Figure 5a). The activation changes in the middle frontal areas resembled the trend in the middle occipital areas during repetitions. The activations in the middle frontal areas were decreasing in the NC group ($F(2, 30) = 7.10, p < .01$), while the activations first decreased in D2 but increased to the similar extent in D3&4 compared with D1 in the MCI group during repetitions ($F(2, 32) = 6.21, p < .01$; Figure 5b). Regarding with the deactivations, the repetition $\times$ group interaction was significant in the IFG ($F(2, 62) = 7.17, p < .01$). The deactivations in the IFG were reducing in the NC group ($F(2, 30) = 6.73, p < .01$), while the reducing extent was greater in the MCI group ($F(2, 32) = 40.53, p < .001$; Figure 5c). There was no significant difference in activation patterns during repetitions in ROIs of the anterior cingulate ($F(2, 62) = 2.87, p = .07$), precuneus ($F(2, 62) = 2.55, p = .11$), and middle temporal gyrus ($F(2, 62) = 1.88, p = .16$) between groups. In both groups, the deactivations were reduced in the anterior cingulate areas, precuneus and middle temporal areas with repetitions.

3.2.3 Correlation with behavioral measures—Correlation analyses were performed in order to test the association between repetition-related brain activities and behavioral performance. Behavioral performance was indexed as RT and correct rejection rate of the distracter stimuli for D1, D2, and D3&4, and brain activities were indexed as MOG activation for D1, D2, and D3&4. The results showed that MOG was negatively correlated with behavioral performance. Specifically, brain activation was positively correlated with RT across all the participants ($r = .51, p < .001$) as well as within the NC ($r = .41, p < .005$) and MCI groups ($r = .61, p < .001$; Figure 6a). In addition, MOG activation was negatively correlated with accuracy rate both across all the participants ($r = -.27, p < .010$) and in the MCI group ($r = -.54, p < .001$), but not in the NC group ($r = .18, p = .216$), possibly due to a ceiling effect of NCs' accuracy rate (Figure 6b). Further, the activation of other ROIs (i.e., middle/inferior frontal gyrus, anterior cingulate, precuneus, and middle temporal gyrus) was found to have no correlation with behavioral performance.

3.2.4 VBM analysis—VBM analysis revealed clear differences in GM in two brain regions. MCIs showed significant GM loss in the middle part of medial frontal lobe (peak MNI coordinates: $x = -58.5, y = 12, z = 33; t = 4.12$; cluster size = 2447) and the lateral frontal and parietal lobes (peak MNI coordinates: $x = -18, y = -7.5, z = 42; t = 3.14$; cluster size = 2177) relative to NCs. Regions with GM atrophy in MCIs did not appear to overlap with regions showing significant group differences in repetition effect. To confirm this observation, we conducted an additional two-sample t test with GM volume of occipital lobe as a covariate, and the results were similar to those without the corrections, indicating the observed functional alterations were independent from the anatomical changes.

4. Discussion

In this study, we examined the repetition effect behaviorally and neurally in older adults who were MCI patients and their age-matched cognitively normal controls using a hybrid DMST. MCIs showed impaired explicit memory performance manifested as having longer total RT and lower correct response rate (i.e., Pr) compared with NCs in general. However, the interactions between group and repetition effect of the distracters were not significant (i.e., the repetition-associated RT and accuracy decrease was seen in both NC and MCI groups), indicating that behavioral repetition-associated function was preserved to some extent in MCI. Critically, the simultaneous decrease in RT and accuracy could be interpreted as an accuracy-RT trade-off. However, accuracy was comparable in D2 and D3&4, whereas the RT was shorter in D3&4 than in D2, indicating the accuracy-RT trade-off cannot fully account for the repetition differences. The patterns of repetition priming in reaction time and accuracy rate of distracters (i.e., non-match stimuli) in our study was similar as the results from a cohort in the US using a similar paradigm but easier task difficulty [32], where the RT and accuracy rate decreased with repetition of distracters in both NCs and MCIs. Together, our results suggest that visual perceptual behavioral priming is largely spared in MCI.

Neurally, however, MCIs showed reduced activation in the middle occipital gyrus and the middle frontal gyrus, which have been implicated in repetition learning in previous studies [18, 33, 34]. That is, repetition-driven activation suppression in occipital regions was aberrant in MCIs (e.g., activation was maintained during the 3rd & 4th repetitions relative to NCs), reflecting an impaired function of repetition priming. The MCI group tended to maintain activation for the stimuli of D3&4 in the middle frontal areas, and they had less deactivation during repetition in the inferior frontal areas, which are brain regions often associated with the default mode network (DMN) [35, 36]. Moreover, these functional alterations were not related with their anatomical decline, since VBM analyses did not reveal any significant difference in local GM between MCIs and NCs.

Using a DMST with repeated face images, researchers found similar patterns of brain activities in which reduced fMRI responses over repetition were observed primarily in the occipital-temporal cortex [18]. Such repetition suppression has been consistently reported in repetition priming tasks in young adults [33, 34, 37]. Here we report new findings that this repetition suppression on brain activities was found compromised in MCI patients. The magnitude of activation in the left middle occipital gyrus and middle frontal gyrus first decreased in D2, resembling NC, but increased to the similar extent in D3&4 compared with D1. Similar neural alterations have been reported with other repetition priming paradigms evaluated in MCI. Johnson et al. [38] examined the dynamic process of encoding novel/repeating face images. Results showed, over seven repetitions, that a decrease in MTL activation was found in NC group, but not in MCI group, suggesting compromised encoding processed in MCI. Using the ERP technique during a semantic categorization task, researchers also found that patients with mild AD have altered repetition effect in late ERP components [39]. One possible explanation for MCIs' reduced repetition-driven activation suppressions in the MOG could be interpreted as a compensation mechanism. Specifically, in the current DMST paradigm participants need to differentiate distracters from targets and

correctly reject them. With repetition, distracters become more and more familiar, potentially increasing the difficulty of correct rejection if the sample stimulus was not clearly maintained in working memory. In that case, MCIs with more cognitive decline relative to NCs might need to engage more effort in perception and recognition processes to reach the same performance as NC, particularly on D3&4. Recently, Cabeza and Dennis [40] proposed that attempted-compensation activity will exhibit an inverted-U relationship with brain decline, such that attempted compensation will be most prominent in those who need it the most, as in MCI patients, but then decline with advanced brain deterioration, as in AD patients.

Other than the activation, the alterations of deactivation with repetition were also different between NCs and MCIs. The deactivation areas in the present task (i.e., inferior/medial frontal gyrus, middle temporal gyrus, and inferior parietal lobule) were brain regions included in the default mode network, which is typically deactivated in task-related fMRI experiments [41, 42]. During repetition, the deactivation of DMN in MCI decreased gradually (i.e., relatively more activity), whereas in NC the typical deactivation pattern was relatively evidenced. Similarly, patients with cognitive impairment do not deactivate the precuneus during memory tasks as healthy individuals do [see 43 for a review]. These abnormal deactivations suggest compromised or decreased brain function activities in DMN [44–46]. MCIs' reduced deactivation in the DMN areas (i.e., IFG) suggests that MCI patients failed to maintain a more active mode of cognitive processing relative to the default mode during repetition. The anterior DMN has often been found to associate with self-referential thoughts and cognitive control [43] and has consistently been implicated in the degenerative process [47]. The deposition of amyloid- β protein may underlie the disruption of DMN even in normal aging. Sheline et al. found that older adults with amyloid- β deposits in the brain exhibited greater disruption in DMN functional connectivity than did individuals without amyloid- β [48]. However, a contrary possibility is that lifetime cerebral metabolism associated with altered DMN activity could predispose cortical regions to AD-related changes, including amyloid deposition, metabolic disruption, and atrophy [49].

Individual difference analysis showed that MOG activity was negatively correlated with behavioral performance in both NC and MCI groups (i.e., more activation in the MOG predicted longer RT and lower accuracy rate). These results suggest that MOG activity could be a potential predictor for repetition priming effects. Within the context of a working memory paradigm, the neural activation in frontal cortex was maintained to some extent during repetition [18], which could play a role in monitoring. Hence, participants were able to differentiate distracters from targets correctly within each trial. Reduction in neural activity with repetition was found primarily in extrastriate cortices. This repetition-driven suppression may reflect a process that enables more efficient processing of stimuli encountered repeatedly during an active working memory search. Thus, reaction time serves as an index of stimulus familiarity, allowing for the efficient rejection of irrelevant distracters.

The findings of this study should be interpreted with the context of some limitations. First, the sample size of this study is small. Correspondingly, the subtypes and the severity of cognitive impairment in MCIs could have a significant impact on patterns of functional

alterations in repetition effect, and this issue should be considered in future studies. In addition, as a cross-sectional study, it is not clear to what extent these repetition-related brain functional alterations are related to the progressive trajectories of the disease. Follow-up longitudinal studies would be required to investigate the relationship of these repetition-related functional changes to the progression to AD. In conclusion, studies on behavioral repetition priming and neural repetition effects in MCI patients have been limited. A more naturalistic hybrid memory paradigm might differently find repetition effect compromise in MCI patients. The repeated rejection of non-matching visual distracters in the context of working memory retrieval is closed to perceptual priming. Even so, we found altered brain activity in MCI patients. Brains of persons with MCI manifested reduced repetition-related suppression in the middle occipital gyrus and middle frontal cortex during repetition of distracters, reflecting functional compensation enabling behavioral equivalence with NCs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

For each memory trial in this delayed match-to-sample task, two sample objects in green borders were initially presented, followed by 12 (or 13) successive test pictures (target or distracter object). D1 stands for the initial presentation of a distracter stimulus (i.e., non-match to either of the sample targets), and so forth for D2, D3, and/or D4.

Figure 2.

Group differences in RTs and accuracy during distracter repetition and in explicit memory performance. (a) RT for the distracters with repetitions in NC and MCI group respectively; (b) Accuracy rate for the distracters with repetitions in NC and MCI group respectively; (c) Total RT for the DMS task in NC and MCI group; and (d) Pr for the DMS task in NC and MCI group, respectively.

Figure 3.
Regions showing activation (in red) and deactivation (in blue) during repetition in NC and MCI group ($p < .05$, corrected).

Figure 4.

Activation regions showing significant group differences during 3rd&4th repetition ($p < .005$, voxel size > 26, AlphaSim corrected; in D1& D2, the NC and MCI group did not have significant activation or deactivation differences).

Figure 5. Mean activations (in red) or deactivations (in blue) within the ROIs from (a) the middle occipital gyrus (MOG), (b) middle frontal gyrus (MFG), and (c) inferior frontal gyrus (IFG) for the D1, D2, and D3&4.

Figure 6.

Correlational analysis of brain responses in middle occipital gyrus (MOG) and behavioral performance. (a) Activations in the left MOG were found to positively correlate with RT, whereas (b) negatively correlate with accuracy rate.

Table 1

Summary of participants' demographic information

	NC	MCI	<i>p</i> value
<i>n</i>	16	17	—
Sex (male/female)	8/8	9/8	.866
Age (years)	68.56±5.76	70.53±4.54	.283
Education (years)	11.75±3.17	9.82±4.63	.176
Self-rating anxiety scale	25.25±4.51	29.08±6.13	.063
ADL	14.19±.54	15.15±2.30	.115
MMSE	28.25±1.39	24.47±3.88	<.010
MoCA	26.19±1.52	19.18±4.45	<.001
CDR	0	0.5	—

Note: NC, normal control; MCI, mild cognitive impairment; ADL, the Activities of Daily Life; MMSE, the Mini-Mental Status Examination; MoCA, the Montreal Cognitive Assessment; CDR, the Clinical Dementia Rating.