

Evidence of Neuronal Compensation During Episodic Memory in Subjective Memory Impairment

Susanne Erk, MD, PhD; Annika Spottke, MD; Alice Meisen, MA; Michael Wagner, PhD; Henrik Walter, MD, PhD; Frank Jessen, MD

Context: Accumulating evidence suggests that the mere subjective feeling of memory impairment in the absence of objective cognitive deficits may precede mild cognitive impairment in the continuum of Alzheimer disease manifestation. Brain imaging studies have provided insights into structural and functional alterations at the clinical stages of dementia and mild cognitive impairment, but the functional characteristics of subjective memory impairment (SMI) are largely unstudied.

Objective: To investigate brain activation during memory tasks in individuals without cognitive impairment who report SMI compared with control subjects without cognitive impairment and without SMI.

Design: Functional magnetic resonance imaging study of episodic memory and working memory.

Setting: Memory outpatient clinic.

Participants: Nineteen participants reporting SMI without cognitive impairment and 20 control individuals without cognitive impairment and SMI.

Main Outcome Measure: Brain activation patterns and performance during an associative face-profession episodic memory task, including encoding, recall, and recognition, and a working memory task.

Results: Compared with the control group, SMI was associated with a reduction in right hippocampal activation during episodic memory recall in the absence of performance deficits. This was accompanied by increased activation of the right dorsolateral prefrontal cortex. No differences in performance and no difference in brain activation during working memory were observed in the SMI group.

Conclusions: These results suggest that SMI is accompanied by functional alterations in hippocampal integrity that reflect early neuronal dysfunction and by compensatory mechanisms that preserve memory performance.

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Author Affiliations:

Department of Psychiatry and Psychotherapy, Division of Mind and Brain Research, Charité–Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany (Drs Erk and Walter); Division of Medical Psychology (Drs Erk and Walter and Ms Meisen) and Departments of Psychiatry and Psychotherapy (Drs Spottke, Wagner, Walter, and Jessen) and Neurology (Dr Spottke), University of Bonn, Bonn, and German Center for Neurodegenerative Diseases, Bonn (Dr Jessen), Germany.

THE CHARACTERIZATION OF predementia syndromes in the course of Alzheimer disease (AD) is crucial when aiming at early intervention. Mild cognitive impairment (MCI), as defined by cognitive impairment in relation to age-, sex-, and education-adjusted norms without impairment of functioning in everyday life, is a widely recognized at-risk condition or prodromal syndrome of dementia.¹ Particularly, MCI with memory impairment (amnestic MCI) has been identified as a precursor of Alzheimer dementia.²

Brain imaging studies have provided insights into structural and functional changes related to different clinical stages of AD. At the clinical stage of dementia, AD is accompanied by reductions in glu-

cose metabolism and by hippocampal and cortical atrophy related to neuronal loss.^{3,4} Atrophy and hypometabolism are also seen in MCI and consistently predict progression to dementia of the AD type.^{3,4} Task-related functional magnetic resonance imaging (fMRI) mostly revealed reduced brain activation of the medial temporal lobe during memory tasks in patients with AD compared with controls.⁵⁻⁷ In some studies,^{5,8-10} this was accompanied by increased activation of frontal brain areas. In individuals with MCI, some studies have also reported hypoactivation of the medial temporal lobe during episodic encoding in the right^{11,12} and bilateral^{7,13} hippocampi. In contrast, other researchers have shown hyperactivation of the left^{14,15} or bilateral¹⁶ hippocampus during encoding of novel items. Studies¹⁷⁻¹⁹ testing brain ac-

tivation during retrieval consistently report reduced activation of the left hippocampal region. Some studies in individuals with MCI have provided evidence of increased activation of the left prefrontal cortex (PFC) during recognition,^{15,19-21} whereas others have shown reduced activation of the left PFC^{17,19,22} during encoding and reduced bilateral PFC activation during encoding^{17,19} and recognition.^{17,18} It is well recognized that different clinical stages and variations in tasks and in task performance may account for these inconsistent results in MCI.

Increasing evidence suggests that the mere subjective feeling of memory impairment with still normal cognitive performance (subjective memory impairment [SMI]) may even precede MCI and dementia in the course of clinical AD manifestation.²³ Longitudinal studies^{24,25} in epidemiologic and research cohorts identified SMI as a predictor of future cognitive decline and dementia. In a recent study²⁶ examining a primary care population, the temporal sequence of SMI followed by amnesic MCI was associated with a dramatic risk increase for dementia, particularly of Alzheimer type. Evidence of AD pathology in SMI has been provided by postmortem investigations²⁷ and by cerebrospinal fluid data.^{28,29} A reduced baseline cerebral metabolic rate for glucose utilization in the hippocampal region predicted decline from normal elderly to AD²⁹ and has been the most significant predictor of SMI status.³⁰ Structural brain imaging in population-based and clinical cohorts provided evidence of mild hippocampal volume reductions in individuals with SMI.³¹⁻³³ A recent study³⁴ using magnetoencephalography revealed increased activation of the dorsal pathway, including the dorsolateral PFC (DLPFC), in a memory task in SMI and suggested a continuum from SMI to MCI.

Based on these studies, there is increasing interest in further understanding the physiologic basis of SMI. Two aspects may be associated with the subjective experience of memory impairment. Regarding performance, SMI may be associated with suprathreshold impairment, that is, mild individual decline with performance at cross-sectional testing still in the expected age-, sex-, and education-adjusted range. The concept of SMI as a suprathreshold impairment is supported by the slightly poorer performance in individuals with SMI than in those without SMI that is observed in large samples of formally unimpaired subjects (eg, see Jessen et al³⁵). On the neuronal level, the experience of SMI may signify an increased effort required to compensate for mild dysfunction, particularly in episodic memory. Evidence of neuronal compensation at the presymptomatic stage of AD is provided by studies in unimpaired individuals at increased genetic risk for AD, such as carriers of the apolipoprotein E4 allele³⁶ and in young carriers of presenilin 1 mutations³⁷ showing hyperactivation in brain regions related to episodic memory tasks.

A recent fMRI study³⁸ using a verbal learning task in a small sample of individuals with SMI reported increased activation of the left PFC during memory encoding that was interpreted as compensatory activation. No activation differences in the medial temporal lobe structures had been observed in this study. In the present study, we tested the hypothesis of altered brain

activation indicating neuronal dysfunction and compensation in SMI using fMRI and a sensitive probe of associative memory that allows examination of different cognitive subprocesses, that is, encoding, recall, and recognition of episodic information. Associative memory tasks, and recall in particular, challenge the “hippocampal type” of memory impairment that is most sensitive for early AD.³⁹ To test the specificity of SMI-related alteration of hippocampal function, we also applied a working memory task as a largely hippocampus-independent cognitive probe. Moreover, we analyzed structural brain imaging data to test for morphometric differences between groups.

METHODS

PARTICIPANTS

Nineteen right-handed individuals with SMI were recruited via the memory clinic of the Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany, where individuals asked for a clinical assessment because of persistent experiences of memory problems. We included only individuals whose spouses or family members perceived very mild memory impairment in everyday life. This approach was applied to increase the validity of SMI because pure self-report may be confounded by factors such as personality styles.⁴⁰ All individuals reported onset of memory impairment within the past 10 years. This time criterion was used to exclude individuals with lifelong memory concerns. Individuals with an identifiable cause of SMI, such as specific medical or psychiatric conditions or the use of medications with known effects on cognition, were excluded. In addition to the report on memory impairment, normal performance on cognitive tests was used as the core criterion for SMI as it is conceptualized herein. Normal cognitive functioning was defined by the Consortium to Establish a Registry for Alzheimer Disease (CERAD) neuropsychological battery using German age-, sex-, and education-adjusted norms (<http://www.memoryclinic.ch>). All individuals with SMI scored within 1.5 SDs on all subtests of the CERAD battery.

Twenty healthy volunteers without any medical or psychiatric disorders or use of medications with known effects on cognition were recruited from the general population. All the individuals scored within 1.5 SDs on all the subtests of the CERAD neuropsychological test battery.¹ None of the participants had a current major depressive episode.

Individual depression-related symptoms were still assessed in all participants using the Beck Depression Inventory (BDI). Demographic and neuropsychological data and BDI scores were analyzed using a commercially available software program (SPSS Statistics 17; SPSS Inc, Chicago, Illinois) and analyses of variance with the factor group. The cognitive measures were compared between groups (using analysis of variance), with age and BDI score as covariates. Sociodemographic and neuropsychological data are given in **Table 1**. The study was approved by the ethics committee of the University of Bonn. After complete description of the study to the participants, written informed consent was obtained.

EXPERIMENTAL DESIGN

Episodic Memory Task

During fMRI, participants completed 3 consecutive memory tasks, that is, encoding, recall, and recognition of face-

Table 1. Demographic and Neuropsychological Description of the Study Sample

Variable	Control Group	SMI Group	Statistic	P Value
Sex, No.				
Female	9	5	$\chi^2=1.48$.22
Male	11	14		
Age, mean (SD), y	66.8 (5.4)	68.4 (5.7)	$F=0.88$.35
Education, mean (SD), y	15.4 (3.4)	14.5 (3.5)	$F=0.40$.69
MMSE score, mean (SD) ^a	29.3 (1.3)	29.1 (1.0)	$F=0.001$.98
Verbal fluency score, mean (SD) ^a	23.5 (5.6)	23.7 (4.8)	$F=0.12$.73
Naming score, mean (SD) ^a	14.9 (0.4)	14.6 (0.8)	$F=4.67$.04
Immediate recall score, mean (SD) ^a	23.6 (2.6)	22.6 (3.5)	$F=0.02$.08
Delayed recall score, mean (SD) ^a	8.6 (1.2)	7.4 (1.8)	$F=3.37$.08
Visual praxis score, mean (SD) ^a	10.9 (0.5)	10.8 (0.5)	$F=0.05$.83
Visual recall score, mean (SD) ^a	9.9 (1.7)	9.5 (2.0)	$F=0.42$.52
TMT A score, mean (SD), s ^a	41 (17.2)	42.9 (24.7)	$F<0.001$	>.99
TMT B score, mean (SD), s ^a	99.4 (45.6)	105.2 (60.2)	$F=0.06$.81
BDI score, mean (SD)	4.3 (3.8)	7.5 (4.9)	$F=5.10$.03

Abbreviations: BDI, Beck Depression Inventory; MMSE, Mini-Mental State Examination; SMI, subjective memory impairment; TMT, Trail-Making Test.

^aIncluding age and BDI score as covariates.

profession pairs, with an overall duration of 13 minutes (eFigure 1 available at <http://www.archgenpsychiatry.com>). These tasks were previously used for imaging associative memory-related hippocampal function in an imaging genetics approach.⁴¹ The encoding task consisted of 16 face-profession pairs and 24 head contours as a control condition, with 4 blocks of 4 face-profession pairs and 4 blocks of 6 head contours each. Face-profession pairs were presented for 6 seconds, and head contours for 4 seconds. Thus, each block lasted 24 seconds. Participants had to imagine the person acting in a scene of the written profession and had to indicate whether the profession suited the presented face to induce deep encoding. During the control condition, participants had to indicate which ear of the depicted head contour was larger. The alternating sequence of 4 face-profession association blocks and 4 control blocks was presented twice to ensure successful encoding. During recall, faces were presented together with the question of whether the depicted person had to complete an apprenticeship or academic studies to qualify for the respective profession that had been learned during encoding. Participants had to indicate by button press which qualification was correct. Stimulus duration and control condition were similar to those during encoding, and blocks were presented only once. For recognition testing, faces were depicted together with 2 written professions, and participants had to indicate which profession was correct. Stimulus duration for recognition was 3 seconds. The control condition consisted of 4 blocks of 4 head contours each (3 seconds). Thus, each recognition block lasted 12 seconds. Similar to during recall, blocks were presented only once.

N-Back Task

To determine the specificity of potential alterations of brain activation in hippocampus-dependent episodic memory processing, we further used a well-validated executive cognition probe, the n-back task. Participants were presented with a series of digits (1-4) presented sequentially for 500 milliseconds (interstimulus interval, 1500 milliseconds). In the 0-back control condition, participants had to press a button corresponding to the digit presently seen. In the 2-back working memory condition, they had to react to the digit seen 2 instances before the present digit. The task consisted of 4 alternating blocks and lasted 5 minutes.

IMAGING PARAMETERS

Imaging was performed using a 3-T Siemens Trio scanner (Siemens Medical Solutions, Erlangen, Germany). Functional MRIs were taken using an echo-planar imaging sequence. Whole-brain coverage was obtained with 33 axially tilted slices (slice thickness, 2.4 mm plus a 0.6-mm gap; field of view, 192 mm; repetition time, 1.96 seconds; echo time, 30 milliseconds; and flip angle, 80°). High-resolution 3-dimensional T1-weighted images were acquired with 160 contiguous sagittal slices 1 mm thick (field of view, 256 mm; repetition time, 1.57 seconds; echo time, 3.42 milliseconds; inversion time, 800 milliseconds; and flip angle, 15°).

FUNCTIONAL IMAGE PROCESSING

Image processing and statistical analyses were conducted using statistical parametric mapping methods as implemented in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) and were similar for all tasks. Briefly, images were realigned to a mean image (movement parameters were confined to <3 mm of translation and <1.7° of rotation between volumes), slice time corrected, spatially normalized to a standard stereotactic space (a brain template created by the Montreal Neurological Institute) with volume units (voxels) of 2 × 2 × 2 mm, smoothed with an 8-mm full-width at half maximum gaussian filter, and ratio normalized to the whole-brain global mean. A first-level fixed-effects model was computed for each participant. Regressors were created from the time course of the 2 experimental conditions (memory, control; 2-back, 0-back) and convolved with a canonical hemodynamic response function. Movement parameters were included in the first-level model as regressors of no interest. For each participant, statistical contrast images of the contrast memory vs control for the respective episodic memory tasks (encoding, recall, and recognition) and images of the contrast 2-back vs 0-back for the working memory task were obtained. In the respective second-level random-effects group analyses (encoding, recall, recognition, n-back), individual regionally specific effects for each participant were compared using a full factorial design (analysis of variance), with group as a factor resulting in a *t* statistic for every voxel. In addition, age and BDI score were used as confounding covariates for statistical analysis. The significance threshold was

Table 2. Task Performance During Scanning

Task	Hit Rate, Mean (SD)		F	P Value
	Control Group	SMI Group		
Recall	0.61 (0.09)	0.57 (0.14)	0.97	.33
Recognition	0.58 (0.12)	0.57 (0.16)	0.05	.83
0-back	0.95 (0.06)	0.96 (0.08)	0.24	.62
2-back	0.42 (0.16)	0.41 (0.22)	0.44	.51

Abbreviation: SMI, subjective memory impairment.

set to $P < .05$, familywise error corrected for multiple comparisons across the whole brain or for multiple comparisons in an anatomically a priori–defined region of interest (hippocampus or DLPFC) provided by Wake Forest University PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>). The rationale for the a priori–defined region of interest is based on the relevance of the hippocampus and the DLPFC for episodic memory and the reported activation differences in these regions between patients with AD and those with MCI compared with healthy individuals.

STRUCTURAL IMAGE PROCESSING

We performed a brain morphometry analysis on T1-weighted structural images using the voxel-based morphometry toolbox provided with SPM5. High-resolution T1-weighted images were checked for scanner artifact and gross anatomical abnormalities. After setting the origin at the anterior commissure, images were segmented using the Hidden Markov Random Field option of the VBM5 segmentation algorithm. Images were normalized to the Montreal Neurological Institute template, and smoothing was applied with 12-mm full-width at half maximum. After preprocessing, we obtained smoothed modulated normalized data, which were incorporated into statistical analysis. Group analysis was performed using an analysis of variance (full factorial model), with group as a factor and age and BDI score as covariates.

RESULTS

BEHAVIORAL PERFORMANCE

Task performance during scanning was analyzed using SPSS Statistics 17. Analyses of variance with the factor group were calculated to determine differences in performance between groups, and age and BDI score were included as covariates (**Table 2** and **Figure 1**). No difference between groups was observed during recall or recognition or during working memory performance.

FUNCTIONAL IMAGING RESULTS

Episodic Memory Task

As detailed in the “Materials and Methods” section, the task included encoding, recall, and recognition of face-profession associations in 3 consecutive sessions, showing highly significant activations in core regions of episodic memory processing (for detailed results by group, see eTable 1). Whereas no significant difference between groups was observed during encoding and rec-

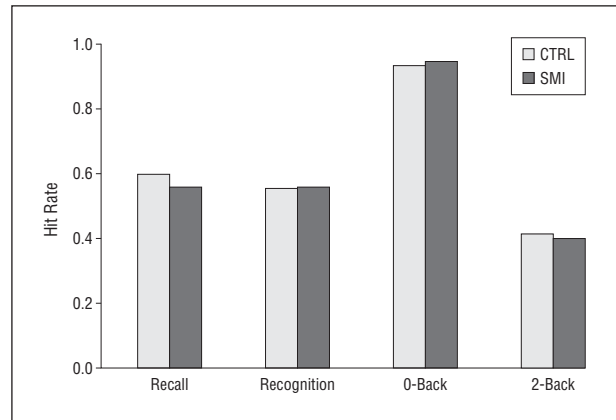


Figure 1. Behavioral performance. Participants with subjective memory impairment (SMI) exhibit no statistically significant differences in behavioral performance compared with controls (CTRL) during episodic memory tests (recall and recognition) and working memory (0-back and 2-back).

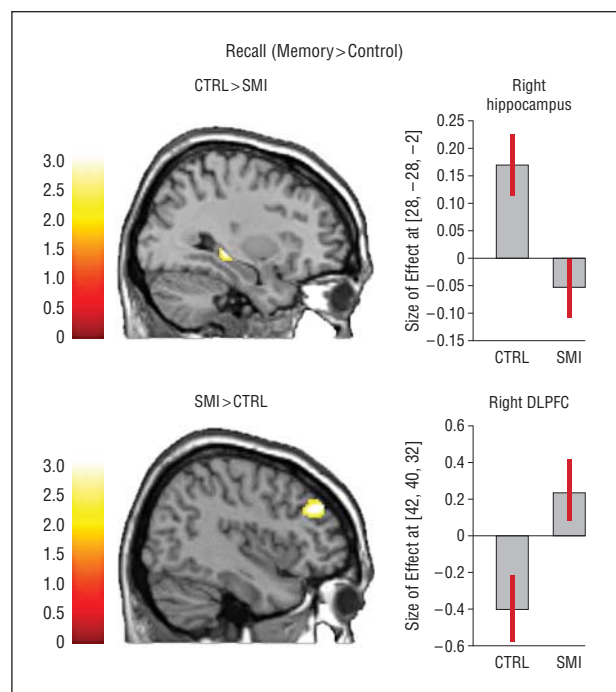


Figure 2. Functional magnetic resonance imaging results. Compared with controls (CTRL), participants with subjective memory impairment (SMI) show significantly reduced activation of the right hippocampus ($x=28$, $y=-28$, $z=-2$; $z=3.14$) and increased right dorsolateral prefrontal cortex (DLPFC) activation ($x=42$, $y=40$, $z=32$; $z=3.16$) during recall. Results were significant at $P < .05$ familywise error corrected for multiple comparisons across the anatomical region of interest (hippocampus or DLPFC). Bar graphs indicate size of effect at the maximally activated voxel in the respective region for the 2 groups.

ognition at the chosen level of significance, the SMI group revealed significantly reduced right hippocampal activation during recall compared with controls ($x=28$, $y=-28$, $z=-2$; $z=3.14$; $P < .05$ familywise error corrected for region of interest) (**Figure 2**). Moreover, compared with controls, the SMI group exhibited in the same recall condition significantly increased activation of the right DLPFC ($x=42$, $y=40$, $z=32$; $z=3.16$; $P < .05$ familywise error corrected for region of interest) (**Figure 2**).

To test for a link between group differences in brain activation and memory performance, we extracted individual beta weights from the peak activated voxel in regions showing a significant group effect during recall, that is, the right hippocampus and the right DLPFC. Beta weights were externally correlated (SPSS Statistics 17) with individual scores in recall and recognition performance. We observed a significant positive correlation between regional activation of the right hippocampus and subsequent recognition performance exclusively in the control group ($r=0.44$, $P=.03$), and, likewise, a significant positive correlation between regional activation of the right DLPFC and subsequent recognition performance exclusively in the SMI group ($r=0.53$, $P=.01$).

N-Back Task

The n-back task, testing for short-term memory processes, revealed highly significant activations in core regions of working memory processing (for detailed results by group, see eTable 2). In this task, no significant differences between groups were observed.

STRUCTURAL IMAGING RESULTS

Voxel-based morphometry analyses revealed no significant volume differences between participants reporting SMI and controls.

COMMENT

In the present study, we tested the hypothesis of altered brain activation in individuals with SMI compared with controls during a cognitive task that sensitively engages hippocampal formation. We found reduced activation of the right hippocampus and increased right DLPFC activation in the SMI group during recall of associative episodic information, which was not accompanied by significant differences in behavioral performance. These data support the hypothesis of altered hippocampal function and concurrent compensatory neuronal mechanisms in SMI.

Whereas studies of hippocampal function in MCI during episodic encoding provided evidence of either hypoactivation or hyperactivation, studies examining episodic retrieval consistently reported reduced hippocampal activation.^{17-19,42} In contrast to the present finding of reduced activation of the right hippocampus during recall in participants with SMI, most studies in patients with MCI found left lateralized hippocampal hypoactivation during retrieval. However, right hippocampal hypoactivation in MCI has consistently been found during encoding. The present finding of right lateralized hippocampal hypoactivation is (also) backed by a recent study⁴³ in rodents suggesting a leftward bias in hippocampal function in engram formation and information transfer and a rightward bias in memory storage and retrieval processes. But still, the issue of laterality in dementia risk syndromes is not fully understood.

Reduced hippocampal activation during recall in individuals with SMI was accompanied by a significant increase in right DLPFC activation. This can be interpreted as compensatory recruitment of the PFC to maintain performance. This interpretation is supported by the finding of a positive correlation between right DLPFC activation during recall and subsequent recognition performance in the SMI group, whereas controls exhibit a similar correlation between recall-related hippocampal activation and subsequent recognition performance. Coupling between the PFC and the medial temporal lobe may facilitate focused attention on behaviorally relevant stimuli processed through reciprocal pathways between these regions.⁴⁴ It has been proposed that prefrontal-hippocampal interactions are particularly crucial during episodic recall and are modulated by cognitive effort during retrieval attempts,^{45,46} with the DLPFC being involved in verification and monitoring of recollected information.⁴⁷ Compensatory activation of regions in the PFC has been described previously in a meta-analysis⁸ of studies in AD, showing that patients with AD additionally recruit areas in the left ventrolateral PFC during encoding and retrieval of episodic information, whereas controls exhibit greater activation of more dorsal and anterior parts of the PFC. Recently, it has been shown that hippocampal volume is negatively correlated with right DLPFC single-photon emission computed tomographic perfusion, indicating an inverse relation between hippocampal integrity and DLPFC perfusion.⁴⁸

Evidence of compensatory PFC recruitment in patients with MCI during retrieval is ambiguous, showing either increased left PFC^{15,19-21} recruitment or reduced activation of bilateral PFCs.^{17,18} The apparent inconsistencies of the reported findings in patients with MCI are as yet unresolved and may relate to differences in paradigms, to the clinical heterogeneity of MCI groups, and to the fact that different areas of the PFC subserve different operations during episodic memory.⁴⁶

In a recent study,³⁸ brain activation during episodic memory was tested in a small sample of individuals with SMI. Encoding of lists of semantically related words, similar to the Deese-Roediger-McDermott paradigm,^{49,50} revealed increased activation of the left PFC in the SMI group compared with the control group. No significant difference between groups was found during retrieval, and no difference in behavioral performance was observed.³⁸ Although these results differ from the present results regarding laterality, which can be related to different stages of episodic memory processing (encoding vs recall) and different tasks used, it nevertheless underlines the putative compensatory involvement of the PFC during memory processing in SMI.

Based on evidence from cognitive neuroscience^{51,52} and on longitudinal studies in patients, impaired recall, specifically deficits in cued recall, have been proposed as the most sensitive indicators of early AD in individuals with MCI. Consequently, a deficit in recall has been included as a core component of the novel research criteria for pre-dementia AD diagnosis.³⁹ The present data complement and expand the concept of recall deficits as core criteria

for the early manifestation of AD, as we show evidence of impaired, but still compensated, hippocampal function in recall in individuals who still perform normally and who may be considered to be in the pre-MCI stage of AD.

To further elucidate the continuum from early SMI to objective MCI, we performed an additional analysis including 10 individuals with MCI (for a detailed description of the sample, see the Appendix). Compared with controls and the SMI group, individuals with MCI show reduced performance during recall. The fMRI analysis revealed reduced activation of the right hippocampus in these participants, similar to the SMI group. In contrast to the SMI group, however, participants with MCI did not exhibit a significant increase in right DLPFC activation (for detailed results, see the Appendix, eFigure 2, and eTable 3 and eTable 4). Within the constraints of the small number and older age of participants with MCI, we interpret this finding as an indication for deficient compensation in the MCI group, characterizing MCI as a stage further in the progression to dementia.

Altered brain activation patterns in the SMI group seem specific for episodic memory because no functional or behavioral differences between the SMI and control groups were observed during the working memory task. Because working memory also crucially involves attentional processes, it is unlikely that diminished attention contributes to the observed hippocampal deficits in participants with SMI in this study.

In this study, all the participants in the SMI group scored within 1.5 SDs on all the subtests on the CERAD neuropsychological test battery according to the age-, sex-, and education-adjusted reference range. Thus, none of the participants with SMI is considered cognitively impaired. Also, individuals with SMI did not differ significantly from the control group on the CERAD memory subtests. However, in the recall tasks of the CERAD neuropsychological test battery, participants with SMI showed a numerically slightly poorer performance than did the control group. This is in agreement with a cohort study³⁵ identifying frequently slightly worse performance in individuals with SMI in episodic memory compared with individuals without SMI, which may indicate supra-threshold episodic memory decline. In addition, we included only individuals with confirmation of SMI by informants. This procedure was chosen to increase the validity of SMI and also may select a slightly more impaired SMI group compared with recruitment without this criterion. On the Clinical Dementia Rating Scale, these individuals with SMI may, therefore, be scored with 0.5 on the memory item, indicating observed very mild memory impairment. On the neuropsychological performance level, however, they were unimpaired and were, therefore, defined as SMI in this study as opposed to MCI, which requires objective impairment on neuropsychological memory tests.

In this study, individuals with SMI exhibited slightly higher scores on the BDI than did control subjects. None of the participants, however, fulfilled the criteria for a major depressive episode. In several studies on SMI, slightly higher scores on depression rating scales have been ob-

served, although the individuals did not have depression (eg, see the studies by Saykin et al³³ and Stewart et al⁵⁴). Studies^{55,56} have highlighted the association of certain personality traits with concerns about memory performance. High rates of critical self-judgment may extend to domains beyond memory and might result in slightly higher ratings on scales with items that may also occur as symptoms of depression. This topic requires further investigation but was not part of the present study. To address the slight variations in BDI scores in the present study, the scores were included as a covariate in the analyses.

We demonstrated that SMI is characterized by reduced hippocampal activation during episodic recall, indicating early hippocampal dysfunction. Recruitment of the right DLPFC is assumed to reflect increased compensatory effort to enable sustained performance in the presence of early pathology. The effect was observed during recall, the cognitive task, which is behaviorally most sensitive for the prediction of dementia in individuals with MCI. The present results further support the concept of SMI as a compensated pre-MCI state in the clinical manifestation of AD.

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Correspondence: Susanne Erk, MD, PhD, Department of Psychiatry and Psychotherapy, Division of Mind and Brain Research, Charité–Universitätsmedizin Berlin, Campus Mitte, Charitéplatz 1, D-10117 Berlin, Germany (susanne.erk@charite.de).

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Online-Only Material: The Appendix, eTables, and eFigures are available at <http://www.archgenpsychiatry.com>.

REFERENCES

1. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman 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. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.
2. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B; International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-1270.
3. de Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Tsui W, Saint Louis LA, Sobanska L, Brys M, Li Y, Rich K, Rinne J, Rusinek H. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Ann N Y Acad Sci*. 2007;1097:114-145.
4. Mosconi L, Brys M, Glodzik-Sobanska L, De Santi S, Rusinek H, de Leon MJ.

- Early detection of Alzheimer's disease using neuroimaging. *Exp Gerontol*. 2007; 42(1-2):129-138.
5. Grön G, Bittner D, Schmitz B, Wunderlich AP, Riepe MW. Subjective memory complaints: objective neural markers in patients with Alzheimer's disease and major depressive disorder. *Ann Neurol*. 2002;51(4):491-498.
 6. Pariente J, Cole S, Henson R, Clare L, Kennedy A, Rossor M, Cipolotti L, Puel M, Demonet JF, Chollet F, Frackowiak RS. Alzheimer's patients engage an alternative network during a memory task. *Ann Neurol*. 2005;58(6):870-879.
 7. Small SA, Perera GM, DeLaPaz R, Mayeux R, Stern Y. Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Ann Neurol*. 1999;45(4):466-472.
 8. Schwindt GC, Black SE. Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. *Neuroimage*. 2009;45(1):181-190.
 9. Rémy F, Mirrashed F, Campbell B, Richter W. Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage*. 2005;25(1):253-266.
 10. Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, Schacter DL, Albert MS. fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2003;74(1):44-50.
 11. Johnson SC, Baxter LC, Susskind-Wilder L, Connor DJ, Sabbagh MN, Caselli RJ. Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. *Neuropsychologia*. 2004;42(7):980-989.
 12. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, Hansen KW, Gleason CE, Carlsson CM, Ries ML, Asthana S, Chen K, Reiman EM, Alexander GE. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. *Neurobiol Aging*. 2006;27(11):1604-1612.
 13. Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, Petersen RC, Boeve BF, Knopman D, Tang-Wai DF, Ivnik RJ, Smith GE, Tangalos EG, Jack CR Jr. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. *Neurology*. 2003;61(4):500-506.
 14. Hämäläinen A, Pihlajamäki M, Tanila H, Hänninen T, Niskanen E, Tervo S, Karjalainen PA, Vanninen L, Soininen H. Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging*. 2007;28(12):1889-1903.
 15. Kircher TT, Weis S, Freymann K, Erb M, Jessen F, Grodd W, Heun R, Leube DT. Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry*. 2007;78(8):812-818.
 16. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, Bertram L, Mullin K, Tanzi RE, Blacker D, Albert MS, Sperling RA. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*. 2005;65(3):404-411.
 17. Mandzia JL, McAndrews MP, Grady CL, Graham SJ, Black SE. Neural correlates of incidental memory in mild cognitive impairment: an fMRI study. *Neurobiol Aging*. 2009;30(5):717-730.
 18. Petrella JR, Krishnan S, Slavin MJ, Tran TT, Murty L, Doraiswamy PM. Mild cognitive impairment: evaluation with 4-T functional MR imaging. *Radiology*. 2006; 240(1):177-186.
 19. Trivedi MA, Murphy CM, Goetz C, Shah RC, Gabrieli JD, Whitfield-Gabrieli S, Turner DA, Stebbins GT. fMRI activation changes during successful episodic memory encoding and recognition in amnesic mild cognitive impairment relative to cognitively healthy older adults. *Dement Geriatr Cogn Disord*. 2008;26(2):123-137.
 20. Gigi A, Babai R, Penker A, Hendler T, Korszyn AD. Prefrontal compensatory mechanism may enable normal semantic memory performance in mild cognitive impairment (MCI). *J Neuroimaging*. 2010;20(2):163-168.
 21. Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, Grodd W. Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging*. 2007;28(3):404-413.
 22. Dannhauser TM, Shergill SS, Stevens T, Lee L, Seal M, Walker RW, Walker Z. An fMRI study of verbal episodic memory encoding in amnesic mild cognitive impairment. *Cortex*. 2008;44(7):869-880.
 23. Reisberg B, Prichep L, Mosconi L, John ER, Glodzik-Sobanska L, Boksay I, Monteiro I, Torossian C, Vedvyas A, Ashraf N, Jamil IA, de Leon MJ. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. *Alzheimers Dement*. 2008;4(1)(suppl 1):S98-S108.
 24. Reid LM, MacLullich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord*. 2006;22(5-6):471-485.
 25. Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement*. 2010;6(1):11-24.
 26. Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer S, Haller F, Kölsch H, Luck T, Mösch E, van den Bussche H, Wagner M, Wolny A, Zimmermann T, Pentzek M, Riedel-Heller SG, Romberg HP, Weyerer S, Kaduszkiewicz H, Maier W, Bickel H; German Study on Aging, Cognition and Dementia in Primary Care Patients Study Group. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry*. 2010;67(4):414-422.
 27. Barnes LL, Schneider JA, Boyle PA, Bienias JL, Bennett DA. Memory complaints are related to Alzheimer disease pathology in older persons. *Neurology*. 2006; 67(9):1581-1585.
 28. Visser PJ, Verhey F, Knol DL, Scheltens P, Wahlund LO, Freund-Levi Y, Tsolaki M, Minthon L, Wallin AK, Hampel H, Bürger K, Pirttilä T, Soininen H, Rikkert MO, Verbeek MM, Spuru L, Blennow K. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol*. 2009;8(7):619-627.
 29. Mosconi L, De Santi S, Li J, Tsui WH, Li Y, Boppana M, Laska E, Rusinek H, de Leon MJ. Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol Aging*. 2008;29(5):676-692.
 30. Mosconi L, De Santi S, Brys M, Tsui WH, Pirraglia E, Glodzik-Sobanska L, Rich KE, Switalski R, Mehta PD, Pratico D, Zinkowski R, Blennow K, de Leon MJ. Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints. *Biol Psychiatry*. 2008; 63(6):609-618.
 31. Tepest R, Wang L, Csernansky JG, Neubert P, Heun R, Scheef L, Jessen F. Hippocampal surface analysis in subjective memory impairment, mild cognitive impairment and Alzheimer's dementia. *Dement Geriatr Cogn Disord*. 2008; 26(4):323-329.
 32. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW, Mutsaers ER, Bollen EL, Admiraal-Behloul F, Westendorp RG, Middelkoop HA. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *J Neurol*. 2004;251(6):671-675.
 33. Jessen F, Feyen L, Freymann K, Tepest R, Maier W, Heun R, Schild HH, Scheef L. Volume reduction of the entorhinal cortex in subjective memory impairment. *Neurobiol Aging*. 2006;27(12):1751-1756.
 34. Maestu F, Baykova E, Ruiz JM, Montejó P, Montenegro M, Llanero M, Solesio E, Gil P, Yubero R, Paul N, Pozo F, Nevado A. Increased biomagnetic activity in healthy elderly with subjective memory complaints. *Clin Neurophysiol*. 2011;122(3): 499-505.
 35. Jessen F, Wiese B, Cvetanovska G, Fuchs A, Kaduszkiewicz H, Kölsch H, Luck T, Mösch E, Pentzek M, Riedel-Heller SG, Werle J, Weyerer S, Zimmermann T, Maier W, Bickel H. Patterns of subjective memory impairment in the elderly: association with memory performance. *Psychol Med*. 2007;37(12):1753-1762.
 36. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med*. 2000;343(7):450-456.
 37. Mondadori CR, Buchmann A, Mustovic H, Schmidt CF, Boesiger P, Nitsch RM, Hock C, Streffer J, Henke K. Enhanced brain activity may precede the diagnosis of Alzheimer's disease by 30 years. *Brain*. 2006;129(pt 11):2908-2922.
 38. Rodda JE, Dannhauser TM, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment: increased prefrontal cortex activation compared to controls during an encoding task. *Int J Geriatr Psychiatry*. 2009;24(8):865-874.
 39. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6(8):734-746.
 40. Carr DB, Gray S, Baty J, Morris JC. The value of informant versus individual's complaints of memory impairment in early dementia. *Neurology*. 2000;55(11): 1724-1726.
 41. Erk S, Meyer-Lindenberg A, Schnell K, Opitz von Boberfeld C, Esslinger C, Kirsch P, Grimm O, Arnold C, Haddad L, Witt SH, Cichon S, Nöthen MM, Rietschel M, Walter H. Brain function in carriers of a genome-wide supported bipolar disorder variant. *Arch Gen Psychiatry*. 2010;67(8):803-811.
 42. Dickerson BC, Sperling RA. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. *Neuropsychologia*. 2008;46(6):1624-1635.
 43. Klur S, Muller C, Pereira de Vasconcelos A, Ballard T, Lopez J, Galani R, Certa U, Cassel JC. Hippocampal-dependent spatial memory functions might be lateralized in rats: an approach combining gene expression profiling and reversible inactivation. *Hippocampus*. 2009;19(9):800-816.
 44. Rempel-Cloer NL, Barbas H. The laminar pattern of connections between prefrontal and anterior temporal cortices in the Rhesus monkey is related to cortical structure and function. *Cereb Cortex*. 2000;10(9):851-865.
 45. Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc Natl Acad Sci U S A*. 1996;93(1):321-325.

46. Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci*. 2003;4(8):637-648.
47. Burgess PW, Shallice T. Confabulation and the control of recollection. *Memory*. 1996;4(4):359-411.
48. Guedj E, Barbeau EJ, Didic M, Felician O, de Laforte C, Ranjeva JP, Poncet M, Cozzone PJ, Mundler O, Ceccaldi M. Effects of medial temporal lobe degeneration on brain perfusion in amnesic MCI of AD type: deafferentation and functional compensation? *Eur J Nucl Med Mol Imaging*. 2009;36(7):1101-1112.
49. Deese J. On the prediction of occurrence of particular verbal intrusions in immediate recall. *J Exp Psychol*. 1959;58(1):17-22.
50. Roediger HL, McDermott KB. Creating false memories: remembering words not presented in lists. *J Exp Psychol Learn Mem Cogn*. 1995;21:803-814.
51. Aggleton JP, Brown MW. Interleaving brain systems for episodic and recognition memory. *Trends Cogn Sci*. 2006;10(10):455-463.
52. Vann SD, Tsivilis D, Denby CE, Quamme JR, Yonelinas AP, Aggleton JP, Montaldi D, Mayes AR. Impaired recollection but spared familiarity in patients with extended hippocampal system damage revealed by 3 convergent methods. *Proc Natl Acad Sci U S A*. 2009;106(13):5442-5447.
53. Saykin AJ, Wishart HA, Rabin LA, Santulli RB, Flashman LA, West JD, McHugh TL, Mamourian AC. Older adults with cognitive complaints show brain atrophy similar to that of amnesic MCI. *Neurology*. 2006;67(5):834-842.
54. Stewart R, Dufouil C, Godin O, Ritchie K, Maillard P, Delcroix N, Crivello F, Mazoyer B, Tzourio C. Neuroimaging correlates of subjective memory deficits in a community population. *Neurology*. 2008;70(18):1601-1607.
55. Jorm AF, Butterworth P, Anstey KJ, Christensen H, Easteal S, Maller J, Mather KA, Turakulov RI, Wen W, Sachdev P. Memory complaints in a community sample aged 60-64 years: associations with cognitive functioning, psychiatric symptoms, medical conditions, APOE genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. *Psychol Med*. 2004;34(8):1495-1506.
56. Jungwirth S, Fischer P, Weissgram S, Kirchmeyr W, Bauer P, Tragl KH. Subjective memory complaints and objective memory impairment in the Vienna-Transdanube aging community. *J Am Geriatr Soc*. 2004;52(2):263-268.