Background: Hippocampal atrophy and reductions in basal cerebral blood volume (CBV), a hemodynamic correlate of brain function, occur with cognitive impairment in Alzheimer disease, but whether these are early or late changes remains unclear. Magnetic resonance imaging is used to assess structure and function in the hippocampal formation.

Objective: To estimate differences in the associations of hippocampal and entorhinal cortex volumes and CBV with memory function in the early and late stages of cognitive impairment by relating these measures to memory function in persons with and without dementia who underwent detailed brain imaging and neuropsychological assessment.

Design: Multivariate regression analyses were used to relate entorhinal cortex volume, entorhinal cortex CBV, hippocampal volume, and hippocampal CBV to measurements of memory performance. The same measures were related to language function as a reference cognitive domain.

Setting: Community-based cohort.

Participants: Two hundred thirty-one elderly Medicare recipients (aged ≥65 years) residing in northern Manhattan, New York.

Main Outcome Measures: Values for entorhinal cortex volume, hippocampal volume, entorhinal cortex CBV, and hippocampal CBV and their relation to memory performance.

Results: No association was noted between entorhinal cortex volume or hippocampal CBV and memory. Decreased hippocampal volume was strongly associated with worse performance in total recall, and lower entorhinal cortex CBV was associated with lower performance in delayed recall. Excluding persons with Alzheimer disease, the association of entorhinal cortex CBV with memory measures was stronger, whereas the association between hippocampal volume and total recall became nonsignificant.

Conclusions: In the early stages of Alzheimer disease or in persons without dementia with worse memory ability, functional and metabolic hippocampal hypofunction contributes to memory impairment, whereas in the later stages, functional and structural changes play a role.

changes in glucose uptake; positron emission tomography, MRI, and single-photon emission computed tomography for basal changes in cerebral blood flow; and MRI for basal changes in cerebral blood volume (CBV). The MRI-based techniques that assess regional CBV, a hemodynamic correlate of oxygen metabolism, have been found to be well suited for imaging the function of the hippocampal formation and its subregions across different species. Previous studies using this technique showed that MRI measures of CBV can detect AD-related hypofunction and that in AD, CBV tightly correlates with positron emission tomography measures of glucose uptake. According to studies using this technique, of all the hippocampal subregions, the entorhinal cortex seems to be the dominant site of hypofunction observed in human and animal AD models.

Whether hippocampal atrophy (presumably related to cell loss) and reduced CBV (a surrogate measure of metabolic deficit) are associated with early or late changes in cognitive impairment remains unclear. We hypothesize that metabolic hypofunction in the hippocampus precedes changes in hippocampal volume.

The objective of this study is to estimate differences in the associations of hippocampal and entorhinal cortex volumes and CBV with memory function in the early and late stages of cognitive impairment by relating these measures to memory function in persons with and without dementia who underwent detailed brain imaging and neuropsychological assessment. Nondemented persons with worse memory function may be at higher risk for dementia.

METHODS

PARTICIPANTS

Participants were selected from a cohort participating in a prospective study of aging and dementia in Medicare recipients 65 years and older residing in northern Manhattan, New York (the Washington Heights/Inwood Columbia Aging Project). These participants were recruited at 2 time points (1992 and 1999) and were followed up at regular intervals of 18 to 24 months. The sampling strategies and recruitment outcomes have been described in detail elsewhere. Recruitment, informed consent, and study procedures were approved by the institutional review boards of Columbia University Medical Center, Columbia University Health Sciences, and the New York State Psychiatric Institute, New York.

This MRI project was concurrent with the second follow-up visit of the cohort recruited in 1992. Participants were deemed eligible for MRI if they did not meet the criteria for dementia at the most recent visit before MRI. Persons with illnesses other than dementia were deemed eligible and, therefore, were included in the study. As described in detail previously, of 769 participants who underwent MRI, 231 (30.0%) underwent, in addition to structural imaging, assessment of entorhinal cortex and hippocampal CBV and, therefore, constituted the final analytic sample. Persons who underwent CBV assessment and who were included in the final sample were more likely to be women (59.3% vs 40.7%) than those excluded from the final sample. No differences were noted in age, apolipoprotein E ε4 (APOE ε4) carrier status, or prevalence of vascular risk factors between included and excluded persons.

CLINICAL ASSESSMENT

At each follow-up evaluation, participants underwent an assessment of medical history, a physical and neurologic examination, and a neuropsychological test battery that included measures of memory, orientation, language, abstract reasoning, and visuospatial ability. Memory was evaluated using the multiple-choice version of the Benton Visual Retention Test and the 7 subsets of the Selective Reminding Test: total recall, long-term recall, long-term storage, continuous long-term storage, words recalled on last trial, delayed recall, and delayed recognition. Orientation was evaluated using parts of the modified Mini-Mental State Examination. Language was assessed using the Boston Naming Test, the Controlled Word Association Test, category naming, and the complex ideational material and phrase repetition subsets of the Boston Diagnostic Aphasia Examination. Abstract reasoning was evaluated using the similarities subtest of the Wechsler Adult Intelligence Scale–Revised and the nonverbal identities and oddities subset of the Mattis Dementia Rating Scale. V岛spatial ability was examined using the Rosen Drawing Test and a matching version of the Benton Visual Retention Test. This neuropsychological test battery has established norms for the same community and has been shown to effectively distinguish between normal aging and dementia.

DIAGNOSIS OF DEMENTIA AND MCI

Diagnosis of dementia and assignment of specific cause was made by consensus of neurologists, psychiatrists, and neuropsychologists based on baseline and follow-up information. Diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria and required evidence of cognitive deficits on the neuropsychological test battery and on evidence of impairment in social or occupational function (Clinical Dementia Rating ≥ 1). Diagnosis of AD was based on the INCDS-ADRDA (NINCDS-ADRDA [National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association]) criteria. Consistent with standard criteria for all subtypes of mild cognitive impairment (MCI), individuals considered for MCI were required to have (1) memory complaint; (2) objective impairment in at least 1 cognitive domain based on the average of the scores on the neuropsychological measures in that domain and a 1.5-SD cutoff value using normative corrections for age, sex, ethnicity, and years of education; (3) essentially preserved activities of daily living; and (4) no dementia. Participants with MCI were stratified into those with (1) isolated impairment in memory or impairment in memory and 1 or more other cognitive domains (amnestic MCI) or (2) no impairment in memory but impairment in 2 or more other cognitive domains (nonamnestic MCI), as described in detail previously.

MAGNETIC RESONANCE IMAGING

Participants underwent imaging using a 1.5-T scanner (Intra; Royal Philips Electronics, Eindhoven, the Netherlands) at Columbia University Medical Center, New York City. For derivation of CBV, we acquired 2 sets of oblique coronal 3-dimensional T1-weighted images (repetition time, 20 milliseconds; echo time, 4.6 milliseconds; flip angle, 25°; in-plane resolution, 0.86 × 0.86 mm; and section thickness, 3 mm) for each participant perpendicular to the hippocampal long axis. The first series of images was acquired before and the second series was acquired 4 minutes after intravenous administration of a standard dose of gadodiamide, 0.1 mmol/kg (Omniscan; GE Healthcare, Ridgewood, New Jersey). For volumetric analysis of the hip-
Hippocampal Volume

The images were transferred electronically to the Imaging of Dementia and Aging Laboratory at the University of California, Davis, for morphometric analysis. Images were analyzed manually using a computer workstation (Ultra 5; Sun Microsystems, Santa Clara, California) by operators unaware of participant status. Before tracing of the hippocampus, the T1-weighted images were reoriented in the coronal plane perpendicular to the long axis of the left hippocampus following procedures described in more detail elsewhere (Figure 1). Briefly, the borders of the hippocampus were traced manually in the coronal orientation with simultaneous monitoring for accuracy in the sagittal and axial orthogonal views. The rostral end of the hippocampus was defined by emergence of the amygdala. In sections in which the uncus was ventral to the caudal amygdala, the uncus was included in the hippocampus. The superior boundary in posterior regions that do not contain amygdala was defined by the hippocampal (choroid) fissure, and the superior portion of the inferior horn of the lateral ventricle formed the superior boundary, excluding fimbria. The inferior boundary of the hippocampus was the white matter of the parahippocampal gyrus. The lateral boundary was the inferior (temporal) horn of the lateral ventricle. The posterior boundary of the hippocampus was the first section in which the fornices were completely distinct from gray and white matter of the thalamus. Interrater reliability in the right and left hippocampi using this method was good (intraclass correlation coefficients of 0.98 and 0.96, respectively).

Entorhinal Cortex Volume

Entorhinal cortex volume determination followed the protocol of Killiany et al and is described in greater detail elsewhere. Briefly, the entorhinal cortex area was manually derived on 3 consecutive coronal images, centered at the level of the mammillary bodies. The outline of the entorhinal cortex region began at the junction of the rhinal sulcus and the surface of the brain. The outline then transected the angle formed by the rhinal sulcus and the inferomedial surface of the brain, cutting across the gray matter to the level of the white matter. The edge of the white matter was then followed to the inferior surface of the hippocampus. The outline continued along the surface of the brain back to the starting point. This procedure was repeated using the same landmarks on the immediately adjacent rostral and caudal slices to calculate the total entorhinal area. Interrater reliabilities for this process averaged 0.90.

Hippocampal CBV Maps

Images acquired for CBV quantification were transferred to a computer workstation containing an analysis software package (MEDx Sensor Systems, Sterling, Virginia). An investigator unaware of participant grouping performed all image processing. To generate CBV maps, the precontrast and postcontrast images were coregistered to each other using an automated image registration program. A GNU plot was generated to assess the quality of the coregistration, and an individual study was rejected if a shift greater than 1-pixel dimension was detected. Three studies (2 in patients with AD and 1 in a control subject) were rejected for poor motion correction. The precontrast image was subtracted from the postcontrast image, and the difference in the sagittal sinus, which serves as an estimate of the image intensity change of 100% blood, was recorded. The subtracted image was then divided by the difference in the 4 pixels with the highest intensity values measured from the sagittal sinus and multiplied by 100, yielding relative CBV maps. The voxel size for these CBV maps was 0.78125 × 0.78125 × 3 mm. As described previously, in the series of oblique coronal images, we consistently found that a section anterior to the lateral geniculate nucleus and posterior to the uncus provides optimal visualization of hippocampal morphologic features and internal architecture. The external structure of the hippocampus was manually traced, as was the internal architecture that follows the hippocampal sulcus and the internal white matter tracts (Figure 2). With the aid of standard atlases, regions of interest of 4 subregions of the hippocampal formation were identified according to the following anatomical criteria: (1) entorhinal cortex: the inferolateral boundary follows the hippocampal sulcus, the medial boundary is the medial aspect of the temporal lobe, and the superior boundary is the entorhinal cortex; (2) subiculum: the medial boundary is the medial extent of the hippocampal sulcus or the horizontal inflection of the hippocampus, the inferior boundary is the white matter of the underlying parahippocampal gyrus, the superior boundary is the hippocampal sulcus, and the lateral boundary is a few pixels medial to the vertical inflection of the hippocampus; (3) CA1 subregion: the medial boundary is 2 to 3 pixels lateral to the end of the subiculum region of interest (approximately at the beginning of the vertical inflection of the hippocampus) and the extension of the hippocampal sulcus/white matter tracts, the inferior boundary is the white matter of the underlying parahippocampal gyrus, and the superior boundary is the top of the hippocampal formation; and (4) dentate gyrus: the medial boundary is the medial extent of the temporal lobe, the inferolateral boundary is the hippocampal sulcus/white matter tracts, and the superior boundary is the top of the hippocampal formation, where the alveus is typically identified.

Because the border zones between any 2 subregions cannot be identified without histologic landmarks, they were excluded from the regions of interest. Mean relative CBV from the region of interest of each hippocampal subregion was measured in each participant and was used for group data analy-
Examination of regional CBV vs regional volumetry yields different information. Examination of regional CBV provides an estimate of the basal metabolic rate, and regional volumetry provides a measurement of parenchymal integrity, or atrophy, due to neuronal or glial loss. Estimates of CBV are derived in voxels representative of each region of interest, whereas volume is calculated by summing across the same regions. Thus, although the 2 approaches differ in the quantification of the region, they are regionally comparable.

Quality Control of MRI Measures

Each image was rated for image quality based on signal to noise ratio, susceptibility artifact, and movement. Those deemed to be of poor quality were not analyzed. Of the 769 images available, 623 were of satisfactory quality to analyze entorhinal cortex volume and 749 were of satisfactory quality to analyze hippocampal volume. After 392 images were dropped from the CBV analysis, 231 were available for this analysis.

APOE Genotyping

The APOE genotypes were determined as described by Hixson and Vernier with slight modification. We classified persons as homozygous or heterozygous for the APOE ε4 allele or as not having the APOE ε4 allele.

STATISTICAL METHODS

First we evaluated the demographic and clinical characteristics of the study sample at baseline. Then we used multivariate regression models to estimate all main effects of entorhinal cortex CBV, entorhinal cortex volume, hippocampal volume, and hippocampal CBV on measures of memory performance, adjusting all of the models for age, sex, ethnicity, and years of education. We focused on measures of total recall and delayed recall because learning and memory are the hallmarks and the most sensitive measures of cognitive impairment in AD. To determine whether potentially observed associations remained consistent in persons without dementia, we then repeated all analyses excluding persons with dementia (n=17). To determine whether potentially observed associations were specific to memory function, we finally repeated all analyses using a language summary score as the outcome, which was derived by a factor analysis of data from all 15 neuropsychological measures in the entire cohort. Main contributors to this language factor score were the Boston Naming Test, the Controlled Oral Word Association Test, and the Wechsler Adult Intelligence Scale–Revised similarities subtest. All data analysis was performed using statistical software (SPSS version 16.0; SPSS Inc, Chicago, Illinois).

RESULTS

Table 1 summarizes the clinical and demographic characteristics of the study sample. The 17 persons with dementia at the time of MRI were included in the study because at the last visit before MRI they were not yet demented and, thus, met the inclusion criteria. Of the 17 persons with dementia, 10 (58.8%) had probable AD without concomitant disease, 4 (23.5%) had probable AD with stroke, and 3 (17.7%) had probable AD with other concomitant disease. Persons with MCI or dementia had, on average, smaller hippocampal volumes and worse
memory function than did persons without cognitive impairment (Table 2).

No association was noted between entorhinal cortex volume or hippocampal CBV and memory as measured by total and delayed recall. However, decreased hippocampal volumes were associated with significantly worse performance in total recall (β [SE] = 26.38 [12.18], P = .03) (Table 3), and lower entorhinal cortex CBV was associated with worse performance in delayed recall (β [SE] = 8.43 [5.11], P = .05).

When we repeated all of the analyses excluding demented persons (n = 17), the strength of the association between entorhinal cortex CBV and delayed recall was increased (β [SE] = 10.92 [4.44], P = .01), whereas the association between hippocampal volume and memory performance was attenuated and was no longer significant (β [SE] = 9.07 [12.01], P = .45) (Table 3). Additional exclusion of persons with MCI (n = 52) subsequently attenuated the association between entorhinal cortex CBV and delayed recall (β [SE] = 10.24 [4.16], P = .02) and further attenuated the association between hippocampal volume and memory performance (β = 2.69 [12.29], P = .83). No associations were noted of entorhinal cortex CBV, entorhinal cortex volume, hippocampal volume, or hippocampal CBV with language performance. When we repeated all of the analyses stratiﬁng by APOE genotype (APOE ε4 carriers vs noncarriers) or brain hemispheres, all of the results were similar across strata.

Magnetic resonance imaging technology provides the opportunity to image functional and structural correlates of changes in the hippocampal formation simultaneously. We investigated the stage at which changes in hippocampal volume, hippocampal CBV, entorhinal cortex volume, and entorhinal cortex CBV best reﬂected changes in memory performance. In a combined group of demented and nondemented persons, lower hippocampal volume was associated with worse total recall, and lower entorhinal cortex CBV was associated with worse delayed recall. When persons with dementia were excluded, however, the association between hippocampal volume and memory was attenuated and nonsignificant, whereas the association between entorhinal cortex CBV and delayed recall became stronger. Additional exclusion of persons with MCI subsequently attenuated the increased association between entorhinal cortex CBV and delayed recall and further attenuated the association between hippocampal volume and memory performance. No associations were noted of entorhinal cortex CBV, entorhinal cortex volume, hippocampal volume, or hippocampal CBV with language performance, suggesting that the observed effects are speciﬁc to the memory domain.

Results of human and animal studies have suggested different stages through which AD progresses: neuronal malfunction manifesting as synaptic or metabolic deﬁcit followed by insoluble protein aggregates typified by amyloid plaques and neurofibrillary tangles and, ﬁnally, by neuronal cell death. At this point, however, this pattern of progression serves only as a working model. The functional and structural stages in AD are not categorically exclusive, and the temporal sequence of malfunction and cell loss is not proved. Structural and functional changes in the hippocampal formation could simultaneously or sequentially contribute to memory impairment. Structural and functional imaging techniques as used in the present study have the potential to help clarify the relation between structural and functional hippocampal changes during the disease and the molecular mechanisms by which these changes lead to memory impairment.

The present findings are consistent with those of previous imaging studies that reported associations between hippocampal volume and entorhinal cortex defects and memory function. After early structural MRI study results showed atrophy of the hippocampus in patients with dementia of moderate severity, later studies found atrophy in patients with milder dementia. Atrophy on MRI is also observed in high-risk populations, such as patients with MCI or those at risk for autosomal dominant familial AD, and in persons without cognitive impairment. In persons without cognitive impairment and in patients with MCI, hippocampal atrophy severity predicts conversion to dementia independently of neuropsychological performance. In the hippocampal formation, the entorhinal cortex was observed to be the region predominantly affected by the effects of AD, and there is evidence that it is superior to hippocampal volume in predicting future cognitive decline.

Functional imaging can, in general, estimate hippocampal dysfunction by mapping disease-related changes in glucose uptake, reflecting glucose metabolism, or by mapping changes in any of the 3 correlates of oxygen metabolism: cerebral blood ﬂow, CBV, and deoxyhemoglobin content. All 4 variables can successfully detect re-
Regional dysfunction in AD. However, MRI maps of CBV are preferable because they are more directly coupled to brain metabolism and give a more accurate functional view of the tissue that may indicate disease via cell dysfunction before cell loss and atrophy. Indeed, previous AD studies have shown that CBV tightly correlates with measures of glucose metabolism, obviating the concern that AD-related vascular abnormality uncouples basal CBV from underlying neuronal function. The finding of an association between lower entorhinal cortex CBV and worse delayed recall in the present study is consistent with a previous CBV study finding that reported that of all hippocampal subregions, the entorhinal cortex is the dominant site of dysfunction observed in humans with AD and J20 mice.

The present study extends previous works in that we explored the effects of hippocampal and entorhinal cortex volume and CBV in affected and unaffected individuals, explored at what stage of cognitive impairment these measures exert their effects on memory performance, and explored whether they are specific for memory function. The exclusion of persons with dementia from the analyses caused the associations between hippocampal volume and memory measures to attenuate, whereas the weak association between entorhinal cortex CBV and delayed recall became stronger. Additional exclusion of persons with MCI subsequently further attenuated the association between hippocampal volume and memory performance and also attenuated the increased association between entorhinal cortex CBV and delayed recall observed after the exclusion of patients with dementia. These findings suggest that in the early stages of disease (MCI) or in nondemented persons, functional and metabolic effects correlate with memory, whereas in the later stages, functional and structural changes are present. This notion is supported by the fact that not only persons with AD but also persons with amnestic MCI had, on average, smaller hippocampal CBVs than did persons without cognitive impairment. Because neuronal dysfunction is, compared with neuronal cell death, considered the disease’s cytopathologic feature most amenable to pharmacologic intervention, this finding has major implications.

A limitation of this study is its cross-sectional nature, which limits the inferences that can be made from the results, and the selection of a subpopulation that limits generalization. Furthermore, we had only 17 patients with dementia, and these cases were mild. It is likely

### Table 2. Memory Function, Hippocampal Volume, Hippocampal CBV, Entorhinal Cortex Volume, and Entorhinal Cortex CBV Across Cognitive Impairment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Memory Performance</th>
<th>Hippocampal Volume</th>
<th>Hippocampal CBV</th>
<th>Entorhinal Cortex Volume</th>
<th>Entorhinal Cortex CBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cognitive impairment</td>
<td>0.25 (0.73)</td>
<td>0.29 (0.06)</td>
<td>0.07 (0.03)</td>
<td>0.008 (0.003)</td>
<td>0.02 (0.01)</td>
</tr>
<tr>
<td>Nonamnestic MCI</td>
<td>0.04 (0.56)</td>
<td>0.29 (0.05)</td>
<td>0.06 (0.03)</td>
<td>0.007 (0.002)</td>
<td>0.01 (0.008)</td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td>−0.81 (0.45)</td>
<td>0.29 (0.06)</td>
<td>0.06 (0.02)</td>
<td>0.008 (0.003)</td>
<td>0.01 (0.008)</td>
</tr>
<tr>
<td>Dementia</td>
<td>−1.44 (0.72)</td>
<td>0.24 (0.05)</td>
<td>0.06 (0.02)</td>
<td>0.006 (0.003)</td>
<td>0.01 (0.006)</td>
</tr>
</tbody>
</table>

Abbreviations: CBV, cerebral blood volume; MCI, mild cognitive impairment.

* Significant at P < 0.05 vs persons without cognitive impairment.

### Table 3. Regression Coefficients Relating Hippocampal Volume, Hippocampal CBV, Entorhinal Cortex Volume, and Entorhinal Cortex CBV to Memory and Language Performance

<table>
<thead>
<tr>
<th>Test</th>
<th>All Persons (N=231)</th>
<th>Persons With Dementia Excluded (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Total recall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal volume</td>
<td>26.38 (12.18)</td>
<td>.03 b</td>
</tr>
<tr>
<td>Hippocampal CBV</td>
<td>26.48 (36.14)</td>
<td>.47</td>
</tr>
<tr>
<td>Entorhinal cortex volume</td>
<td>−177.23 (299.39)</td>
<td>.49</td>
</tr>
<tr>
<td>Entorhinal cortex CBV</td>
<td>37.32 (79.96)</td>
<td>.64</td>
</tr>
<tr>
<td><strong>Delayed recall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal volume</td>
<td>1.19 (0.71)</td>
<td>.09</td>
</tr>
<tr>
<td>Hippocampal CBV</td>
<td>3.36 (2.03)</td>
<td>.10</td>
</tr>
<tr>
<td>Entorhinal cortex volume</td>
<td>−2.93 (14.99)</td>
<td>.85</td>
</tr>
<tr>
<td>Entorhinal cortex CBV</td>
<td>8.43 (4.51)</td>
<td>.05 b</td>
</tr>
<tr>
<td><strong>Language performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal volume</td>
<td>0.65 (0.64)</td>
<td>.31</td>
</tr>
<tr>
<td>Hippocampal CBV</td>
<td>−2.09 (1.92)</td>
<td>.28</td>
</tr>
<tr>
<td>Entorhinal cortex volume</td>
<td>8.94 (13.77)</td>
<td>.52</td>
</tr>
<tr>
<td>Entorhinal cortex CBV</td>
<td>4.45 (4.25)</td>
<td>.29</td>
</tr>
</tbody>
</table>

Abbreviations: β, regression coefficient; CBV, cerebral blood volume.

* All models are adjusted for age, sex, education, race, and apolipoprotein E status.

b Significant at P < .05.
that inclusion of more persons with dementia and patients with more severe dementia would have increased the power of the study and would have led to stronger associations. Important strengths of the study include the detailed structural and functional MRI measures with CBV assessment and the detailed neuropsychological test battery, especially designed for diagnosis of cognitive impairment and dementia. To our knowledge, this is the first study to explore and demonstrate the relation between structural and functional (para)hippocampal changes in cognitive impairment and to demonstrate the specificity of this effect for the memory domain.

Mapping a temporal, cognitive, and molecular pattern of hippocampal hypofunction is an important step toward a greater mechanistic understanding of the AD disease process. These findings set the stage for future studies to focus on the molecular level of analysis. Studies are needed to clarify the mechanisms that underlie the observed temporal course of structural and functional molecular changes in the hippocampal formation.

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