Mild cognitive impairment (MCI) is a condition that greatly increases the likelihood of the development of Alzheimer disease (AD), with an annual conversion rate from MCI to AD of 6% to 25%. We undertook this study to investigate the cognitive significance of biomarkers associated with MCI by asking 2 questions: 1) Can levels of CSF tau proteins and amyloid beta 42 peptide (Aβ42) explain thinning of the cerebral cortex in MCI? It has been argued that volumetric temporal and hippocampal atrophy (MCI by asking 2 questions: 1) Can levels of CSF tau proteins and amyloid beta 42 peptide explain thinning of the cerebral cortex in patients with MCI? 2) How are brain morphometry, CSF biomarkers, and apolipoprotein E (APOE) allelic variation related to episodic memory function in MCI?

MATERIALS AND METHODS: Hippocampal volume and cortical thickness were estimated by MR imaging and compared for patients with MCI (n = 18) and healthy controls (n = 18). In addition, regions of interest (ROIs) were selected in areas where the MCI group had atrophy and which overlapped with the episodic memory network (temporal, entorhinal, inferior parietal, precuneus/posterior cingulate, and frontal). Relationships among morphometry, CSF biomarkers, APOE, and memory were tested. The analyses were repeated with an independent sample of patients with MCI (n = 19).

RESULTS: Patients with MCI and pathologic CSF values had hippocampal atrophy. However, both patients with pathologic and patients with nonpathologic CSF had a thinner cortex outside the hippocampal area. CSF pathology was related to hippocampal volume, whereas correlations with cortical thickness were found mainly in one of the samples. Morphometry correlated robustly with memory performance across MCI samples, whereas less stable results were found for tau protein.

CONCLUSION: The differences in hippocampal volume between the MCI and the healthy control groups were only found in patients with pathologic CSF biomarkers, whereas differences in cortical thickness were also found for patients without such pathologic features. Morphometry in areas in the episodic memory network was robustly correlated with memory performance. It is speculated that atrophy in these areas may be associated with the memory problems seen in MCI.
formed consent. Patients with no problems with activities of daily living in a university-based clinic were assessed for inclusion, all giving informed consent. The project was approved by a committee for medical research ethics. Patients aged 40 to 70 years, 450 ng/L or more for ≤50 years, 500 ng/L or more for >70 years, Aβ42 >80 ng/L, and Aβ42 < 500 ng/L. The participants were tested for APOE e4 alleles, and scored as presence of 0, 1, or 2 e4 alleles. The number of patients with pathologic CSF biomarkers and distribution of APOE e4 alleles is presented in Table 2. There was large overlap between pathologic features for P-tau and T-tau, and the 2 variables were combined to 1 tau score (pathologic versus nonpathologic).

**Methods**

**Sample**

Sample characteristics are presented in Table 1. The project was approved by a committee for medical research ethics. Patients aged 40 to 79 years with MCI were included for at least 6 months attending a university-based clinic were assessed for inclusion, all giving informed consent. Patients with no problems with activities of daily living, symptoms lasting 6 months or longer, Global Deterioration Scale score of 3 to 5, and Mini-Mental State Examination score of 23 or greater were included. Criteria for exclusion were established psychiatric disorder, cancer, drug abuse, solvent exposure, or anoxic brain damage. The first 18 patients (sample 1) were scanned on 1 MR scanner and the next 19 (sample 2), on another. Practical reasons imposed the change of scanner. Neuropsychology data for 2 participants from sample 1 are missing because 1 patient did not wish to participate further after the imaging and lumbar puncture were done, and 1 did not receive this examination because of insufficient coordination in the initial phases of the project. Healthy volunteers without deficits related to memory, emotionality, and tempo (primarily spouses of the patients) were included as controls. All controls were scanned at the same scanner as sample 1, and thus all comparisons between controls and patients with MCI are based on sample 1. In addition, 6 controls were scanned on both scanners. This was done for comparison of data from the 2 scanners. As seen from Tables 1 and 2, the 2 MCI samples were very similar.

**Lumbar Puncture and Laboratory Analyses**

Patients, but not controls, underwent lumbar puncture, examined for CSF biomarkers for degenerative brain disease (T-tau, P-tau, and Aβ42) with commercially available kits (Innogenetics, Belgium) adapted to a Robotic Microplate 150 Processor (Tecan, Switzerland). Lumbar puncture was not performed in 1 patient in sample 1 because of recent back surgery and low back pain. The criteria for pathologic values were as follows: T-tau, 300 ng/L or more for ≤50 years, 450 ng/L or more for >50 years, 500 ng/L or more for >70 years, P-tau, >80 ng/L, and Aβ42 < 500 ng/L. The participants were tested for APOE e4 alleles, and scored as presence of 0, 1, or 2 e4 alleles. The number of patients with pathologic CSF biomarkers and distribution of APOE e4 alleles is presented in Table 2. There was large overlap between pathologic features for P-tau and T-tau, and the 2 variables were combined to 1 tau score (pathologic versus nonpathologic).

**MR Imaging Scanning and Analyses**

**Sample 1.** A Symphony 1.5T MR scanner (syngo MR 2004A 4VA25A software) with a conventional quadrature head coil was used (Siemens, New York, NY). The pulse sequences used for morphometric analysis were two 3D magnetization-prepared rapid acquisition of gradient echo (MPRAGE), T1-weighted sequences in succession (TR, 2730 ms; TE, 3.19 ms; TI, 1100 ms; FA, 15°; matrix, 256 × 192). Each volume consisted of 128 sagittal sections with a thickness of 1.33 mm and in-plane resolution of 1.0 mm × 1.33 mm.

**Sample 2.** An Espree 1.5T MR scanner (syngo MR B13 4VB13A software) (Siemens) was used, with the following sequences: Two 3D MPRAGE, T1-weighted sequences in succession (TR, 2400 ms; TE, 3.65 ms; TI, 1000 ms; FA, 8°; matrix, 256 × 192), 160 sagittal sections with thickness of 1.2 mm, and in-plane resolution of 1 × 1.2 mm. The 2 MPRAGES were averaged to increase the signal-to-noise ratio. MR segmentations were performed with FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). The procedures for automated thickness measurement are described elsewhere and are validated by histology and MRI. Scans were also segmented to yield volumetric data for the hippocampal formation, including the dentate gyrus, cornu ammonis (CA) fields, subiculum/parasubiculum, and the fimbria. Hippocampal volume was calculated as the sum of the left and right hippocampal volume, regressed on intracranial volume (ICV). SPSS 15.0 (SPSS, Chicago, Ill) was used for the rest of the analyses.

**Memory Testing**

The Rey Auditory-Verbal Test (RAVLT) was used to measure episodic memory in the patients. A total of 15 words are read aloud to the patient, who subsequently recalls as many words as possible. This is repeated 5 times with the same list (learning trials). Next, an interference list is presented and to be recalled before the patient is requested to recall the first list without its being read again. After 30 minutes, the patient is asked to recall the first list of words again with no re-reading. This trial is termed 30 minutes recall. The number of correct responses on the 5 learning trials is summed to 1 learning score. To limit the number of statistical tests performed, we analyzed only the learning score and the 30 minutes recall score.

**Statistical Analyses**

First, ICV-corrected hippocampal volume was compared between the control and MCI groups from sample 1 by an independent samples t test. Next, cortical thickness across the brain surface was compared between the groups by use of a general linear model approach. This was done to identify areas where those with MCI have probable atrophy, and additional analyses were restricted to areas of difference, which also overlapped reasonably well with the above-described episodic memory network. To control for false-positives as a result of multiple comparisons, we used a false-discovery rate correction.
pathologic CSF biomarker, and APOE were correlated with RAVLT learning and 30 minutes recall in the 2 MCI samples independently. The significant relationships were then retested by partial correlations controlling for the effects of age. All analyses were run separately in sample 1 and sample 2, and the results compared. This was done to test the stability of the results and the validity of the method.

Results

Correlations Across Scanners
Volumes of hippocampus, cortex, and the lateral ventricles were estimated for the 6 healthy controls who were scanned on both scanners and correlated across scanners. The Pearson coefficients were of 0.99, 0.90, and 0.999 (all P < .05), respectively. Mean differences in cortical thickness were generally within ± 0.1 mm across the brain surface. This indicates that change of scanner did not introduce much bias in the data.

Morphometry Comparisons Between MCI and Healthy Control Groups
Both ICV-corrected (t [34] = 2.70; P = .011; MCI, −0.41; controls, 0.41) and raw (t [34] = 2.24; P = .032; MCI, 7689 mm³; SD, 1550; controls, 8615 mm³; SD, 828) hippocampal volumes were significantly smaller in MCI sample 1 than in the healthy controls. Additional analyses were done with ICV-corrected volume. Figure 1 shows a scatterplot with hippocampal volume for patients and controls. Figure 2 shows the results of the cortical comparisons, and scatterplots are presented in Fig 3. There was bilateral thinning of the cerebral cortex in MCI in large areas, especially in the temporal cortex, inferior parietal, and medial parietal areas, and partly in the superior and inferior frontal areas. A strong effect was observed in the right and a weaker in the left hemisphere extending from the posterior cingulate to precuneus. As can be seen from Fig 4, the distribution of P values is shifted to the left (thicker cortex in controls), with almost no voxels to the right of the midline (thicker cortex in MCI). This indicates that it is very unlikely that the effect of MCI on cortical thickness is a result of false-positives from multiple statistical comparisons.

To test whether probable atrophy could be found also in participants without pathologic CSF biomarker values, hippocampal volume and the ROIs from Fig 3 were entered into one-way ANOVAs with 3 groups (controls, MCI without pathologic CSF biomarkers, MCI with pathologic CSF biomarkers). There was a main effect of group for all variables except for the left hemisphere precuneus (P = .12) and right hemisphere superior frontal gyrus (P = .06). Post hoc testing with Bonferroni corrections for multiple comparisons showed that patients with MCI and pathologic CSF biomarkers had significantly smaller hippocampal volume than the controls, whereas this was not found for patients with MCI without pathologic values (P = .66). For the cortical ROIs, differences between the control and MCI groups without pathologic CSF were found in the left hemisphere inferior parietal cortex (P < .05), with a trend toward significance for the entorhinal cortex (P = .071) and in the right hemisphere inferior parietal gyrus, entorhinal cortex, and precuneus (P < .05) and a trend for the middle temporal gyrus (P = .073).
Correlations Between CSF Biomarkers, APOE Status, and Brain Morphometry

Table 3 presents the results of ANOVAs testing the relationships between CSF biomarkers, APOE status, and the different morphometry variables. Figure 5 illustrates scatterplots of selected relationships. In general, stronger associations were observed in sample 2 compared with sample 1. The hippocampus was related to tau in both samples, as was the left and right inferior parietal and entorhinal gyri in sample 2 and the left middle temporal gyrus in sample 1. Aβ42 and APOE were only related to morphometry in sample 2: the hippocampus and precuneus in both hemispheres, and the left entorhinal gyrus for Aβ42; and the left and right entorhinal gyri, in addition to the right precuneus, for APOE.

The significant relationships were retested with age as a covariate. In sample 1, the relationships between the tau and the hippocampus survived. In sample 2, the association between tau pathology and the left and right inferior parietal gyri and the right entorhinal gyrus survived, as did the relationships among Aβ42 and the hippocampus, the left and right precuneus, and the left entorhinal gyrus.

Correlations Between Psychometric Memory Performance and Brain Morphometry

Mean scores for RAVLT learning and 30 minutes recall was 33.6 (SD, 11.99) and 5.9 (SD, 3.7) in sample 1, and 32.7 (SD, 10.2) and 5.7 (SD, 3.7) in sample 2. Correlations between memory scores and the biomarkers are presented in Table 4 and scatterplots in Fig 6. Of the 10 morphometry variables, 5 and 6 correlated significantly with RAVLT learning in samples 1 and 2, respectively, whereas 3 showed a trend toward significance ($P < .06$). The correlations with RAVLT 30 minutes recall were much smaller in sample 1, where 1 reached significance and 1 showed a trend. In sample 2, the same 6 variables correlated with 30 minutes recall and learning, in addition to the inferior parietal gyrus and middle temporal gyrus. Tau correlated significantly with both learning and 30 minutes recall in sample 2. The significant relationships were then retested by partial correlations controlling for the effects of age.
In sample 2, the hippocampus and entorhinal gyrus still correlated with both learning and 30 minutes recall, whereas tau correlated with 30 minutes recall.

**Discussion**

There are 2 main findings in our study: 1) Although the patients with pathologic CSF biomarker levels (but not the patients with nonpathologic levels) had smaller hippocampal volume than controls, differences in cortical thickness were found also in patients with MCI without pathologic CSF biomarkers. 2) Episodic memory correlated with morphometry in areas overlapping with the episodic memory network.

**Can levels of CSF tau proteins and Aβ42 explain thinning of the cerebral cortex in MCI?** Our results indicate that especially tau-pathology is related to reductions in hippocampal volume in MCI. The findings of a reduced hippocampus in MCI are in accordance with previous reports, but the new finding was that this difference depended on the participants with pathologic CSF biomarkers. This fits with knowledge that tau-related pathologic features (neurofibrillary tangles) are initially limited to the hippocampus, the entorhinal cortex, and adjacent limbic structures, whereas amyloid deposition is more distributed.

Our data are in accordance with recent results showing widespread cortical thinning in MCI. The current sample is small, but the similarity of findings indicates that the results probably are valid. The thinning was quite symmetric across hemispheres and was located mainly in the temporal (lateral and medial) and inferior parietal cortices, in addition to parts of the superior frontal cortex and some more scattered medial parietal and frontal effects. In several ROIs, differences between patients and controls did not depend on the patients with pathologic CSF biomarkers. Thus, these data indicate that patients with pathologic CSF levels alone do not account for the group effect of a thinner cortex in MCI. It seems that tau-related pathologic features strike the hippocampus aggressively, as indicated by de Leon et al., but cannot account for all cortical atrophy in MCI.

When the brain areas that distinguished the patients from the controls were related directly to the CSF biomarkers and APOE status, it was found that tau was related to 2 of the 10 ROIs in sample 1 and 5 in sample 2. Aβ42 was related to none of the ROIs in sample 1 but 4 in sample 2, and APOE status was related to 3 ROIs in sample 2. In general, the effects were stron-

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**Table 3: Effects of CSF biomarkers and APOE on brain morphometry**

| ROI                          | Sample 1 | Sample 2 | Tau | Aβ42 | APOE |
|------------------------------|----------|----------|-----|------|------|
| hippocampus                  |          |          | S1  | S2   | F    |
| A: Middle temporal LH        |          |          | .51† | .18† | .04  |
| B: Inferior parietal LH      |          |          | .18† | .51† | .04  |
| C: Entorhinal LH             |          |          | .18† | .51† | .04  |
| D: Precuneus (toward isthmus) |          |          | .18† | .51† | .04  |
| E: Superior frontal LH       |          |          | .18† | .51† | .04  |
| A: Middle temporal RH        |          |          | .18† | .51† | .04  |
| B: Inferior parietal RH      |          |          | .18† | .51† | .04  |
| C: Entorhinal RH             |          |          | .18† | .51† | .04  |
| D: Precuneus (toward isthmus) |          |          | .18† | .51† | .04  |
| E: Superior frontal RH       |          |          | .18† | .51† | .04  |

Note: — indicates Sample 1; † indicates pathologic biomarkers; ‡ indicates pathologic compared to nonpathologic; F ratio, Pearson r.

— F ratio, Pearson r.

**Table 4: Correlations between biomarkers and episodic memory**

| Biomarker | Sample 1 | Sample 2 | Tau | Aβ42 | APOE |
|-----------|----------|----------|-----|------|------|
| RAVLT Learning |          |          | S1  | S2   | F    |
| A: Middle temporal LH |          |          | .51† | .28† | .22 |
| B: Inferior parietal LH |          |          | .51† | .28† | .22 |
| C: Entorhinal LH |          |          | .51† | .28† | .22 |
| D: Precuneus (toward isthmus) |          |          | .51† | .28† | .22 |
| E: Superior frontal LH |          |          | .51† | .28† | .22 |
| A: Middle temporal RH |          |          | .51† | .28† | .22 |
| B: Inferior parietal RH |          |          | .51† | .28† | .22 |
| C: Entorhinal RH |          |          | .51† | .28† | .22 |
| D: Precuneus (toward isthmus) |          |          | .51† | .28† | .22 |
| E: Superior frontal RH |          |          | .51† | .28† | .22 |

Note: — indicates Sample 1; † indicates pathologic biomarkers; ‡ indicates pathologic compared to nonpathologic; F ratio, Pearson r.

— F ratio, Pearson r.
ger in sample 2, but the relationship between the hippocampus and tau pathologic features was replicated across samples. The relationship between tau and hippocampal volume is well known, but relationships between tau pathologic features and thickness in widespread cortical areas, to our knowledge, have not been reported previously. The discrepant findings across the 2 samples indicate that these effects are not very robust, however. Still, although relationships between tau pathologic features and cortical thickness in selected ROIs were found in the patients from sample 2, group differences in thickness existed also independently of this pathologic process. Longitudinal data are needed to better assess the effects of tau pathologic features on the cortical morphometry in MCI.

How are brain morphometry, CSF biomarkers, and APOE related to episodic memory function in patients with MCI? There were 7 of the 10 morphometry variables that correlated with the learning score in at least 1 of the samples, whereas 5 of these were significant or near significant in both samples. For instance, the entorhinal gyrus and precuneus in the left hemisphere correlated with learning in both samples, whereas the hippocampus correlated strongly in sample 2 and was marginally significant in sample 1. These are core structures in the episodic memory network. In sample 2, there was an almost perfect correspondence between the results for learning and 30 minutes recall, indicating that atrophy in the episodic memory network in MCI affects both learning and 30 minutes’ recall performance.

Of the CSF biomarkers, tau pathologic features correlated with learning and recall in sample 2. Correlations between tau and memory have been found previously. Aβ42 and APOE did not correlate with memory performance in either of the samples. Thus, it seems that morphometry and episodic memory correlated robustly across samples, whereas the results for tau are less stable.

Our results indicate that the differences in morphometry within the MCI group have cognitive correlates. Several of the brain areas with probable atrophy in MCI correlated with memory function. Buckner suggested that dysfunction of a neural network including the medial temporal lobe and the precuneus, extending into the posterior cingulate and retrosplenial cortex, may be central in explaining the memory deficits associated with AD. In our study, morphometric differences and correlations with episodic memory were identified in these areas, indicating that atrophy here contributes to the memory problems seen in MCI. However, the effect of age is substantial on both brain morphometry and episodic memory function, and the results should be replicated with larger patient groups of same-age patients.

**Limitations**
Previous knowledge about the episodic memory network guided the selection of the ROIs, but the exact placement and size of each were based on where controls and patients with MCI differed in thickness. This was done to ensure that the ROIs reflected brain areas where the patients are likely to have atrophy and thus are areas relevant for the disease. However, exact definition of the ROIs a priori would be a more solid approach. The samples were scanned on different scanners, which may potentially lead to biased results. However, the replication of the results across the 2 samples makes this less likely and increases the generalizability of the conclusions. Furthermore, it has been shown that the segmentation approach used in our study yields thickness estimates that brain-behavior relationships that are highly reliable across different scanner platforms. The original voxel resolution was not identical between the 2 scanner platforms (1.0 × 1.33 mm vs 1.0 × 1.2 mm). Still, the high correlations between the estimated volumes of the different structures indicate that this difference did not introduce much bias in the data and that the results across samples can be compared. Another point relates to the relatively small difference in cortical thickness between participants. However, histologic validation studies have shown that the measurement error associated with the approach used is approximately 0.25 mm, which is clearly less than the differences reported in our study.

**Conclusion**
The main conclusions from our data are that although reduction of hippocampal volume in MCI was found only in patients with pathologic CSF biomarkers, group differences in cortical thickness existed even in the absence of these biomarkers. Furthermore, brain morphometry in several ROIs correlated with episodic memory performance. The sample in our study was small, and the results must thus be interpreted with
caution. The findings should be replicated with larger patient populations and longitudinal data. Still, the replication of the results across samples suggests reliability of the results.

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