Supporting Information

Wolk et al. 10.1073/pnas.1001412107

SI Materials and Methods

Participants. Data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60-million, 5-year public–private partnership. Its primary goal has been to test whether imaging measures, biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD.

For the present analysis, we selected patients with a baseline diagnosis of AD ($n = 193$), further limited to patients who had cerebrospinal fluid testing consistent with AD [t-tau/amyloid β ($A\beta)_{1–42} \geq 0.39$] as previously established in ADNI and an autopsy-based dataset (1), and then divided into those with at least one APOE ε4 allele ("carriers", $n = 67$) and those without ("noncarriers", $n = 24$). AD diagnosis was made using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria (2). Other inclusion and exclusion criteria are described at http://www.adni-info.org/.

Psychometric Testing. We examined baseline cognitive testing that included, in part, the Mini-Mental State Examination (3), Rey Auditory Verbal Learning Test (AVLT) (4), the Trail Making Test [Trails A and Trails B (5)], Digit Symbol Substitution Test (6), Digit Span (6), category fluency test [Animals and Vegetables (7)], and Boston Naming Test (8). On the basis of prior work suggesting a greater memory deficit in ε4 carriers, we were particularly interested in examination of the AVLT, which allows for fractionation of different aspects of episodic memory. The AVLT consists of five learning trials in which a list of 15 words is read and the subject is asked to immediately recall as many items as possible. After an interference list of 15 novel words is read and recalled, subjects are then asked to recall words from the initial list (5-min delayed recall). A 30-min delayed recall trial and recognition test follow. For the recognition test, subjects are presented with a list of the 15 studied words and 15 nonstudied foils and are asked to circle all words previously studied. To account for false alarms (FA) to nonstudied items, we calculated a measure of discriminability, d-prime (d′), in a standard fashion based on classic signal detection theory (9). Because d′ is undefined when either proportion is 0 or 1, we used standard formulas to convert these values: Hits = (no. of hits + 0.5)/(no. of studied items + 1) and FA = (no. of FA + 0.5)/(no. of unstudied items + 1).

MRI Imaging and Analysis. MRI scans were collected on 1.5-T scanners using a standardized protocol. For the present analysis, the magnetization-prepared rapid gradient echo sequence was used with the following characteristics: sagittal plane, repetition time/echo time/inversion time 2,400/3/1,000 ms, flip angle 8°, 24 cm field of view, 192 × 192 in-plane matrix, and 1.2-mm slice thickness (10).

The primary T1 analysis procedures have been described in detail and applied and validated in a number of publications and presentations (11). T1 image volumes were examined quantitatively by a cortical surface-based reconstruction and measurement of cortical thickness, which was then analyzed using two complementary approaches. First we examined group differences in the thickness of regions of interest (ROIs) previously determined to be reliably associated with AD, constituting the "cortical signature" of AD (12, 13). Unlike most ROI analyses, these regions were defined in a data-driven manner based on analysis of several datasets, as opposed to being determined strictly by anatomic boundaries. These ROIs encompass the following regions: rostral medial temporal cortex (perirhinal and entorhinal), rostral inferior temporal gyrus, temporal pole, angular gyrus, supramarginal gyrus, superior parietal lobule, precuneus, superior frontal gyrus, and inferior frontal sulcus/caudal middle frontal gyrus. These ROIs were defined in a previous publication (12) and are localized on the average template cortical surface and then mapped using the surface-based spherical registration technique described previously to each individual (11, 14–16). We have previously shown that the localization of cortical ROIs defined in such a manner is highly reproducible across individuals (17–19); for example, the ROI on the rostral medial temporal cortex is on the crown of the uncal parahippocampal cortex extending down into the collateral sulcus very reproducibly, encompassing entorhinal and perirhinal cortices as they are typically defined using manual skilled operator tracing protocols. Given its prominence in AD pathology, hippocampal volume was also determined and normalized to intracranial volume as previously described (20). In addition to the ROI approach, an exploratory analysis across the entire cortical mantle was pursued.

Statistical Analysis. Between-group comparisons of psychometric and neuroimaging variables were calculated by univariate analysis of covariance (ANCOVA). Although there was not a clear difference in age and disease severity between carriers and noncarriers, these factors, along with years of formal education, were included as covariates in all group comparisons of psychometric measures. Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) was used as the metric for disease severity. In ANCOVAs of a priori anatomic ROIs, age and CDR-SB were entered as covariates. Stepwise linear regression analyses were performed to relate each psychometric measure that differed between the two groups to MRI data. Age, years of formal education, and group status (carrier, noncarrier) were entered into the models, and ROIs from the neuroimaging analysis served as independent variables. Statistical analyses were performed using SPSS 16.0.

Statistical analysis of the whole-cortex comparison was performed as described previously using a general linear model (12, 13). Because the goal of this exploratory analysis was to comprehensively survey the entire cortex for subtle effects of interest related to APOE genotype, a relatively liberal statistical threshold was used, $P < 0.1$ uncorrected.

1. Shaw LM, et al.; Alzheimer's Disease Neuroimaging Initiative (2009) Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 65:403–413.
2. McKhann G, Drachman D, Folstein M, Katzman R, Price D (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944.
3. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198.
4. Rey A (1964) *L'examen Clinique en Psychologie* (Presses Universitaires de France, Paris).
5. Reitan R (1958) Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 8:271–276.
6. Wechsler D (1981) *WAIS-R. Wechsler Adult Intelligence Scale-Revised* (Psychological Corporation, New York).

7. Butters N, Granholm E, Salmon DP, Grant I, Wolfe J (1987) Episodic and semantic memory: A comparison of amnesic and demented patients. *J Clin Exp Neuropsychol* 9:479–497.

8. Kaplan E, Goodglass H, Weintraub S (1983) *The Boston Naming Test* (Lea and Feibiger, Philadelphia).

9. Snodgrass JG, Corwin J (1988) Pragmatics of measuring recognition memory: applications to dementia and amnesia. *J Exp Psychol Gen* 117:34–50.

10. Jack CR, Jr, et al. (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging* 27:685–691.

11. Fischl B, et al. (2004) Automatically parcellating the human cerebral cortex. *Cereb Cortex* 14:11–22.

12. Dickerson BC, et al. (2009) The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* 19:497–510.

13. Bakkour A, Morris JC, Dickerson BC (2009) The cortical signature of prodromal AD: Regional thinning predicts mild AD dementia. *Neurology* 72:1048–1055.

14. Fischl B, et al. (2008) Cortical folding patterns and predicting cytoarchitecture. *Cereb Cortex* 18:1973–1980.

15. Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9:195–207.

16. Fischl B, Sereno MI, Tootell RB, Dale AM (1999) High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8:272–284.

17. Dickerson BC, et al. (2009) Differential effects of aging and Alzheimer's disease on medial temporal lobe cortical thickness and surface area. *Neurobiol Aging* 30:432–440.

18. Dickerson BC, et al. (2008) Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. *Neuroimage* 39:10–18.

19. Feczko E, Augustinack JC, Fischl B, Dickerson BC (2009) An MRI-based method for measuring volume, thickness and surface area of entorhinal, perirhinal, and posterior parahippocampal cortex. *Neurobiol Aging* 30:420–431.

20. Buckner RL, et al. (2004) A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 23:724–738.

Table S1. Control-referenced *z* scores of cortical signature and hippocampal ROIs

ROI	APOE ε4 carriers (*n* = 49)	APOE ε4 noncarriers (*n* = 20)
Hippocampus	−2.10 (0.95)	−1.37 (1.72)*
MTL	−2.57 (1.52)	−2.19 (1.60)
SFG	−0.74 (0.97)	−1.22 (0.85)[†]
ITG	−1.40 (1.26)	−1.67 (0.92)
IFS	−0.81 (0.89)	−1.02 (0.98)
SPL	−0.58 (1.04)	−1.15 (1.20)[‡]
Precuneus	−0.91 (1.1)	−1.55 (1.36)[‡]
TP	−1.10 (1.33)	−1.40 (1.36)
AG	−1.10 (1.02)	−1.81 (1.29)[‡]
SMG	−1.10 (0.92)	−1.38 (1.21)
Mean thickness	−1.14 (1.09)	−1.66 (1.11)[§]

Values are presented as mead (SD). MTL, rostral medial temporal cortex; SFG, superior frontal gyrus; ITG, rostral inferior temporal gyrus; IFS, inferior frontal sulcus/caudal middle frontal gyrus; SPL, superior parietal lobule; TP, temporal pole; AG, angular gyrus; SMG, supramarginal gyrus.
*$P < 0.01$.
[†]$P = 0.07$.
[‡]$P < 0.05$.
[§]$P = 0.06$.