

# Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers

Jay Nierenberg,<sup>1,4,CA</sup> Nunzio Pomara,<sup>2,4</sup> Matthew J. Hoptman,<sup>3,4</sup> John J. Sidtis,<sup>2,4</sup> Babak A. Ardekani<sup>1,4</sup> and Kelvin O. Lim<sup>5</sup>

<sup>1</sup>Center for Advanced Brain Imaging; <sup>2</sup>Geriatric Psychiatry Program; <sup>3</sup>Division of Clinical Research, The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962; <sup>4</sup>Department of Psychiatry, New York University School of Medicine, 550 First Avenue, New York, NY 10016; <sup>5</sup>Department of Psychiatry, University of Minnesota, 2450 Riverside Avenue, Minneapolis, MN 55454, USA

<sup>CA</sup>Corresponding Author and Address: nierenbe@nki.rfmh.org

Received 25 March 2005; accepted 24 May 2005

Apolipoprotein E  $\epsilon 4$  is a major genetic risk factor for Alzheimer's disease, but the neurobiological basis for this risk is unknown. We used diffusion tensor imaging to measure diffusion anisotropy in the parahippocampal gyrus white matter in healthy elderly apolipoprotein E  $\epsilon 4$  carriers and noncarriers. We also measured volumes of the lateral ventricles and temporal horns as proxies of cerebral atrophy. The  $\epsilon 4$  carriers ( $n=14$ ) showed significantly lower fractional anisotropy and higher radial diffusivity in the

parahippocampal white matter 15 mm below the anterior commissure–posterior commissure plane than noncarriers ( $n=15$ ). No group differences in ventricular volumes were found, nor were diffusion tensor imaging measures modulated by ventricular volumes. Diffusion tensor imaging may be sufficiently sensitive to detect preclinical brain changes related to Alzheimer's disease. *NeuroReport* 16:1369–1372 © 2005 Lippincott Williams & Wilkins.

**Key words:** Alzheimer's disease; Diffusion tensor imaging; Magnetic resonance imaging; Parahippocampal gyrus; Temporal lobes

## INTRODUCTION

The only established susceptibility gene for the more common, late-onset, sporadic form of Alzheimer's disease (AD) is a polymorphism in the gene encoding apolipoprotein E (ApoE) [1,2]. *APOE*  $\epsilon 4$  is associated with earlier symptom onset [1] and, in nondemented individuals, *APOE*  $\epsilon 4$  is associated with higher rates of cognitive decline [3] and temporal lobe atrophy [4]. Postmortem studies have shown higher frequencies of  $\epsilon 4$  in young study participants with early neurofibrillary pathology [5]. Thus, healthy *APOE*  $\epsilon 4$  carriers may help elucidate preclinical biomarkers for AD.

AD has traditionally been considered a disease of the gray matter, despite evidence that the white matter atrophies significantly during AD progression [6]. Demyelination is widespread in advanced AD and its distribution parallels the topography of hallmark AD lesions [7]. Diffusion tensor imaging (DTI) can provide information about white matter microstructure *in vivo*. DTI quantifies the magnitude and direction of tissue water mobility in three dimensions. The diffusion tensor is modeled as an ellipsoid with symmetry across any one of its three axes. The largest axis or eigenvalue ( $\lambda_1$  or  $D_{ax}$ ) reflects the net intravoxel diffusion of water parallel to axon fibers. The minor eigenvalues ( $\lambda_2, \lambda_3$ ) represent diffusion perpendicular to fibers and are typically averaged ( $D_{ra}$ ). Fractional anisotropy (FA) is derived from the eigenvalues and reflects overall white matter integrity. Conditions in which axial diffusion ( $D_{ax}$ ) predominates over radial diffusion ( $D_{ra}$ ), such as in white matter, give rise to high FA, while conditions in which  $D_{ax}$

and  $D_{ra}$  are more similar result in lower FA, such as in gray matter.

DTI and diffusion-weighted imaging (DWI) have been used to demonstrate abnormalities in AD [8–12], including mild dementia [9,12,13]. Recently, Choi *et al.* [14] found decreased frontal FA and increased  $D_{ra}$  in AD, consistent with myelin pathology [15]. Here, we report evidence of disrupted white matter microstructure in the parahippocampal gyrus (PHG) in healthy elderly *APOE*  $\epsilon 4$  carriers. We measured volumes of the lateral ventricles (LVs), including the temporal horns (THs), as proxies of global and temporal lobe atrophy, respectively.

## MATERIALS AND METHODS

All procedures took place at the Nathan Kline Institute (NKI, Orangeburg, New York, USA). Twenty-nine healthy adults, aged 60–75 years and free of dementia and psychiatric illness, participated. Participants were free of significant medical illness and underwent physical examination, electrocardiogram and routine laboratory studies. Exclusion criteria were contraindications for magnetic resonance imaging, history of seizures, head trauma with loss of consciousness, neurological disorder and history of alcohol or other drug dependence. All participants scored  $\geq 28$  on the Mini Mental State Exam (MMSE) and had a Clinical Dementia Rating of 0. Study procedures were approved by the NKI Institutional Review Board and all participants provided written, informed consent. *APOE*

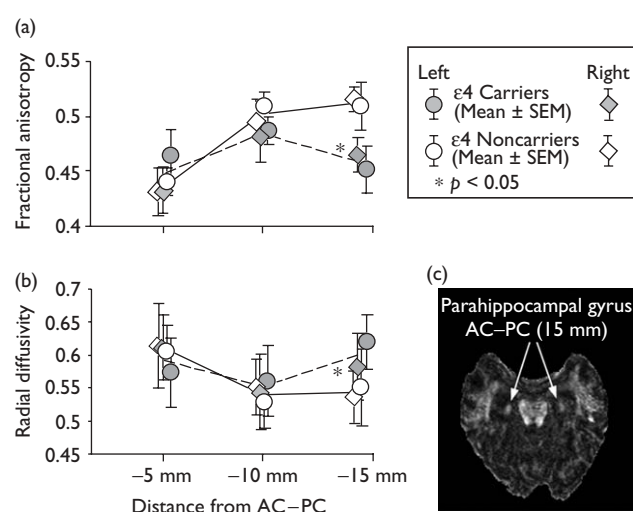
genotyping was performed as previously described [16]. All participants underwent a neurocognitive battery consisting of well validated tests: the Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, Buschke Verbal Memory Test and Purdue Pegboard Test.

**Magnetic resonance image acquisition:** Three sequences were acquired on a 1.5 T Siemens Vision System (Erlangen, Germany): a magnetization-prepared gradient echo scan (MPRAGE; TR/TE=11.4/4.9 ms, matrix=256×256, FOV=300 mm, NEX=1, 1.17 mm slice thickness, 172 slices, no gap), a turbo spin echo scan (TSE; TR/TE=5000/22,90 ms, matrix=256×256, FOV=224 mm, NEX=1, 5 mm slice thickness, 26 slices, no gap) and DTI [14]. The MPRAGE provided T<sub>1</sub>-weighted images and the TSE provided T<sub>2</sub>-weighted and proton density images. DTI (TR/TE=6000/100 ms, matrix=128×128, FOV=240 mm, 5 mm slice thickness, 20 slices, no gap) was acquired using a double echo pulse that has been shown to minimize eddy current effects [17]. Six diffusion-weighted volumes ( $b=1000$  s/mm<sup>2</sup>, four averages) and one without diffusion weighting ( $b=0$  s/mm<sup>2</sup>, two averages) were acquired. DTI and TSE were anterior commissure–posterior commissure (AC–PC) aligned and coregistered at acquisition.

**Image processing:** DTI images were processed using custom software. The diffusion tensor and eigenvalues ( $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$ ) were calculated, from which maps of fractional anisotropy (FA) and trace diffusivity ( $D_{tr}$ ) maps were derived.  $D_{ra}$  maps were generated by averaging  $\lambda_2$  and  $\lambda_3$ . Blind to  $\epsilon 4$  status, square regions of interest (ROIs) (70.3 mm<sup>3</sup>) were placed on DTI maps in the right and left white matter of the PHG, in slices –5 mm, –10 mm and –15 mm relative to the AC–PC slice (<http://rsb.info.nih.gov/ij/>). FA maps and T<sub>2</sub>-weighted images guided placements. The white matter of the PHG is easily recognized on FA images (Fig. 1c). After placement, ROIs were transferred to spatially registered positions on maps of  $D_{tr}$ ,  $D_{ax}$  and  $D_{ra}$ . Intraclass correlation coefficients (two raters, eight cases) for the ROI placement method were 0.8 or higher for all ROIs and were 0.99 for each of the ROIs at AC–PC –15 mm.

**Lateral ventricle volume measurement:** MPRAGE images were used to create a mask of the intracranial contents and obtain total intracranial volume. Masked MPRAGE images were used to automatically classify voxels into gray matter, white matter, cerebrospinal fluid and a fourth compartment, consisting of partial volumes of gray matter and cerebrospinal fluid (<http://www.fmrib.ox.ac.uk/fsl>). The MPRAGE images and segmentation output were realigned in all three dimensions and edited slice-by-slice (<http://www.slicer.org>). ROI delineation involved separating the body of the LV from the third ventricle at the foramina of Monro and separating the TH from the trigone of the LV [18]. A single rater (J.N.) measured all cases and a second rater (M.J.H.) edited five cases. Interrater reliability coefficients of 0.986 or higher were obtained for each of the ROIs.

**Data analysis:** For each DTI map (FA,  $D_{tr}$ ,  $D_{ax}$  and  $D_{ra}$ ), repeated-measures ANOVA was performed. Genotype was a between-participants factor; region and side were within-participant factors. Age and education effects were tested with ANCOVA. Persistent significant effects of genotype



**Fig. 1.** Line graphs showing group means for (a) fractional anisotropy (FA) and (b) radial diffusivity ( $D_{ra}$ ). Group means are plotted against the region of the parahippocampal gyrus in which measurements were taken, relative to the anterior commissure–posterior commissure (AC–PC) plane. Left-sided measures are depicted as diamonds and right-sided measures as circles. Connecting lines [dashed for apolipoprotein E (APOE)  $\epsilon 4$  carriers] are right–left averages. Error bars are SEM. (c) FA map at AC–PC –15 mm showing position of the parahippocampal white matter.

were followed up with two-tailed *t*-tests. Significance was  $p < 0.05$ .

Absolute volumes and relative volumes (absolute volumes divided by intracranial volume) of the TH and LV (i.e. the combined volume of the frontal horns, body, occipital horns and trigone) were tested with Mann–Whitney *U*-tests, because of several violations of normality. Associations between DTI and ventricular volume were tested with Pearson moments; log transformations of relative volumes were used, as this normalized the distribution of the measures. Age-corrected TH volumes were the residuals from least-square linear regression of transformed relative volumes on age.

## RESULTS

Groups were well matched on demographic and cognitive variables (Table 1). The only significant difference between groups was a higher reverse digit span score [ $t(27)=2.574$ ,  $p=0.016$ ] in the  $\epsilon 4$  carriers. Ventricular volumes are shown in Table 2. LV and TH volumes were similar between groups. Although TH volumes correlated significantly with age, age-corrected TH volumes also did not differ across groups (data not shown). Scatter plots for relative TH volume plotted against age showed no evidence that genotype differentially modulated age effects on TH volume.

For all DTI measures, there were no main effects of genotype or side. However, we observed regional effects of genotype for FA and  $D_{ra}$  (Fig. 1a and b). For FA, we observed an effect of region [ $F(2,54)=11.04$ ,  $p < 0.001$ ] and a region by genotype interaction [ $F(2,54)=4.06$ ,  $p=0.023$ ]. Follow-up *t*-tests revealed FA differences at AC–PC –15 mm. At this level, mean FA showed a significant difference on the left [ $t(27)=2.61$ ,  $p=0.015$ ] and a trend effect on the right [ $t(27)=1.882$ ,  $p=0.071$ ]. Omnibus ANOVA for  $D_{ra}$  showed an effect of region [ $F(2,54)=7.94$ ,  $p < 0.001$ ] and a region by genotype interaction [ $F(2,54)=3.86$ ,  $p < 0.027$ ]. Post-hoc *t*-tests showed  $D_{ra}$  differences at AC–PC –15 mm (Fig. 1b).

**Table 1.** Demographic, cognitive and clinical features of study participants.

	APOE ε4 carriers	APOE ε4 noncarriers
n	14	15
M:F	6:8	5:10
Genotype		
ε2ε4	1	—
ε3ε4	11	—
ε4ε4	2	—
ε2ε3	—	5
ε3ε3	—	10
Age (years) <sup>a</sup>	67.7 (5.0)	66.5 (8.1)
Education (years) <sup>a</sup>	15.3 (2.2)	16.1 (2.6)
Handedness (left/right)	1/13	1/14
Family history of AD (no/yes)	8/6	10/5
MMSE <sup>a</sup>	29.6 (0.6)	29.1 (0.9)
WAIS-R vocabulary score <sup>a</sup>	10.9 (1.7)	12.0 (2.5)
WMS-R general memory index <sup>a</sup>	114.2 (14.2)	113.3 (11.9)
Digit span forward score <sup>a</sup>	8.2 (2.2)	9.0 (2.3)
Digit span reverse score <sup>a,*</sup>	6.1 (1.2)	7.7 (2.0)
Buschke total score <sup>a</sup>	70.1 (17.0)	69.7 (14.1)

MMSE: Mini Mental Status Exam; WAIS: Wechsler Adult Intelligence Scale-Revised; WMS-R: Wechsler Memory Scale-Revised.

<sup>a</sup>Mean (SD).

\* $p \leq 0.05$  difference between groups.

**Table 2.** Absolute and relative<sup>a</sup> volumes of lateral ventricles.

Measure	Group mean (in ml) (SD)		U	$p^b$
	Carriers	Noncarriers		
Intracranial volume	1509 (183)	1499 (125)	101.0	0.88
Absolute LV <sup>c</sup>				
Left	13.4 (6.4)	15.6 (10.5)	101.0	0.88
Right	14.1 (6.7)	14.3 (8.4)	99.0	0.81
Total	29.3 (13.6)	31.7 (19.2)	101.0	0.85
Absolute TH <sup>d</sup>				
Left	0.89 (0.43)	0.90 (0.56)	95.0	0.68
Right	0.98 (0.48)	0.91 (0.37)	99.5	0.81
Total	1.87 (0.88)	1.81 (0.92)	101.0	0.88
Relative LV <sup>c</sup>				
Left	0.89 (0.40)	1.01 (0.58)	97.0	0.75
Right	0.93 (0.40)	0.93 (0.47)	102.0	0.91
Total	1.82 (0.92)	1.94 (1.01)	104.0	0.98
Relative TH <sup>d</sup>				
Left	0.06 (0.03)	0.06 (0.03)	105.0	1.00
Right	0.06 (0.03)	0.06 (0.02)	99.0	0.81
Total	0.12 (0.05)	0.12 (0.05)	101.0	0.88

<sup>a</sup>Corrected for intracranial volume  $\times 100$ .

<sup>b</sup>Mann-Whitney test (two-tailed): APOE ε4 carriers versus noncarriers.

<sup>c</sup>LV=frontal horn, body, occipital horn and trigone.

<sup>d</sup>TH=temporal horn.

The repeated-measures ANOVA for  $D_{tr}$  showed an effect of region [ $F(2,54)=4.55$ ,  $p=0.015$ ] and a region by side interaction [ $F(2,54)=3.17$ ,  $p=0.050$ ]. Follow-up paired  $t$ -tests comparing right and left  $D_{tr}$  measures collapsed across genotype groups showed a significant right-greater-than-left asymmetry for  $D_{tr}$  at AC-PC  $-15$  mm [ $t(28)=0.221$ ,  $p=0.035$ ], but no significant laterality effects at other levels. This effect was not strongly driven by either  $D_{ax}$  or  $D_{ra}$ . Omnibus ANOVA for  $D_{ax}$  showed an effect of region [ $F(2,54)=10.87$ ,  $p<0.001$ ] but no interactions with genotype. No association was found between digit span scores and

right, left or averaged measures of FA,  $D_{tr}$ ,  $D_{ax}$  or  $D_{ra}$  at AC-PC  $-15$  mm. For all covariates examined (age, years of education and their combination), the regional effects of genotype observed for FA and  $D_{ra}$  remained significant.

Though ε4 carriers and noncarriers showed no differences in ventricular volumes, the possibility remained that differential regional atrophy might explain the effects in DTI measures. Correlations between log-transformed volumes and each DTI measure ipsilateral to the ventricular ROIs (eight tests per side) were evaluated for measures at AC-PC  $-15$  mm in each participant group and for the cohort as a whole. No correlation approached significance. Thus, neither FA nor  $D_{ra}$  deficits in ε4 carriers were related to the degree of global or temporal lobe atrophy in these participants.

## DISCUSSION

We have shown that the white matter of the PHG is abnormal in healthy carriers of the APOE ε4 allele using DTI. White matter deficits were present in the ventral PHG, consistent with the topography of early neurofibrillary pathology [19]. Thus, white matter anisotropy and diffusivity deficits in ε4 carriers may relate to the neuropathological changes of AD. These findings also suggest that preclinical changes in the white matter of the PHG may be useful for the early detection of AD, using DTI.

DTI studies have shown abnormal white matter integrity in patients with AD [8–12,14,20] and minimal cognitive impairment [9,12,13]. However, this is the first known report of diffusion anisotropy differences in healthy older adults at higher risk for AD. Bozzali *et al.* [8] found reduced FA and increased mean diffusivity in AD relative to controls in the corpus callosum and white matter of the frontal, temporal and parietal lobes. Rose *et al.* [9] obtained similar results for the splenium, cingulum and superior longitudinal fasciculus. Recently, Choi *et al.* [14] reported decreased FA and increased  $D_{ra}$  in the superior frontal white matter of AD patients. Yoshiura *et al.* [10] reported correlations between MMSE scores and  $\lambda_3$  measures in the posterior cingulum, suggesting a functional relationship between radial diffusivity and cognitive function.

The eigenvalues of the diffusion tensor have greater neuropathological specificity than FA or  $D_{tr}$ . Whereas decreased  $D_{ax}$  has been associated with axonal degeneration [21], increased  $D_{ra}$  has been associated with ischemic [15] and developmental [22] myelin lesions. In each case, measures of diffusion anisotropy were decreased, but the eigenvalues differentiated the pathological etiology. In the present study, we observed reduced FA in ε4 carriers secondary to increased  $D_{ra}$ , consistent with selective disruption of, or developmental defect in, a radial diffusion barrier such as myelin. ApoE mediates the transport of cholesterol, phospholipids and their fatty acids in the central nervous system, particularly during neuronal repair. Though oligodendrocytes synthesize the majority of myelin lipids *de novo*, it is not known whether apolipoproteins contribute to local lipid homeostasis. APOE ε4 could disrupt the local lipid environment or reduce the normal clearance of β-amyloid peptides, augmenting their neurotoxicity. Roher *et al.* [23] reported increased amyloid peptides, and reduced cholesterol and myelin proteins in the white matter of the postmortem AD brain, possibly modulated by the APOE genotype.

Braak and Braak [7] have suggested that the vulnerability of brain regions to develop AD neuropathology is related to the timing of normal myelogenesis. Myelinopathy in AD could be caused by elevated levels of amyloid peptides. Song *et al.* [24] reported that mice overexpressing amyloid precursor protein had a DTI profile similar to that reported here. Their study suggests that amyloid deposition may be associated with myelin damage, and it demonstrates a relationship between amyloid deposition and  $D_{\text{rad}}$  supporting the present results.

Although we did not find a relationship between ventricular volume and DTI measures, it might be argued that volumetric assessment of the temporal gray matter may have produced different results. The absence of increased ventricular volume in  $\epsilon 4$  carriers argues against the possibility that cerebrospinal fluid contamination contributed to the results. Though we made every effort to exclude gray matter from our measurements by using small ROIs, white matter atrophy resulting in partial volume effects in the  $\epsilon 4$  carriers might have contributed to our findings. However, we might have expected such an effect to manifest as reduced  $D_{\text{ax}}$ , which was not the case.

Both AD risk [1] and medial temporal lobe volume changes [25] are related to the number of *APOE*  $\epsilon 4$  alleles present. The presence of only two  $\epsilon 4/\epsilon 4$  homozygotes in the cohort prevented us from evaluating this in our study participants. Larger-scale longitudinal DTI studies and neuropathological correlation will be necessary to relate the observed diffusion profile to AD risk and to evaluate its sensitivity and specificity for predicting disease progression.

## CONCLUSION

Using DTI we found abnormal white matter integrity in the PHG of healthy elderly participants with a major genetic risk factor for AD and no evidence of regional or global atrophy. DTI may be sufficiently sensitive to detect AD neuropathology before the onset of symptoms and should be evaluated in a longitudinal context to fully characterize its potential role in the early diagnosis of AD.

## REFERENCES

1. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; **261**:921–923.
2. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS *et al.* Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993; **90**:1977–1981.
3. Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF *et al.* Cognitive change and the APOE epsilon 4 allele. *Nature* 2002; **418**:932.
4. Moffat SD, Szekely CA, Zonderman AB, Kabani NJ, Resnick SM. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. *Neurology* 2000; **55**:134–136.
5. Ghebremedhin E, Schultz C, Braak E, Braak H. High frequency of apolipoprotein E epsilon 4 allele in young individuals with very mild Alzheimer's disease-related neurofibrillary changes. *Exp Neurol* 1998; **153**:152–155.
6. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol* 1986; **19**:253–262.
7. Braak H, Braak E. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. *Acta Neuropathol (Berl)* 1996; **92**:197–201.
8. Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G *et al.* White matter damage in Alzheimer's disease assessed *in vivo* using diffusion tensor magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 2002; **72**:742–746.
9. Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M *et al.* Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *J Neurol Neurosurg Psychiatry* 2000; **69**:528–530.
10. Yoshiura T, Mihara F, Ogomori K, Tanaka A, Kaneko K, Masuda K. Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. *NeuroReport* 2002; **13**:2299–2302.
11. Bozzao A, Floris R, Baviera ME, Apruzzese A, Simonetti G. Diffusion and perfusion MR imaging in cases of Alzheimer's disease: correlations with cortical atrophy and lesion load. *Am J Neuroradiol* 2001; **22**:1030–1036.
12. Hanyu H, Sakurai H, Iwamoto T, Takasaki M, Shindo H, Abe K. Diffusion-weighted MR imaging of the hippocampus and temporal white matter in Alzheimer's disease. *J Neurol Sci* 1998; **156**:195–200.
13. Fellgiebel A, Wille P, Muller MJ, Winterer G, Scheurich A, Vucurevic G *et al.* Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. *Dement Geriatr Cogn Disord* 2004; **18**:101–108.
14. Choi SJ, Lim KO, Monteiro I, Reisberg B. Diffusion tensor imaging of frontal white matter microstructure in early Alzheimer's disease: a preliminary study. *J Geriatr Psychiatry Neurol* 2005; **18**:12–19.
15. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 2003; **20**:1714–1722.
16. Pomara N, Willoughby LM, Hashim A, Serhsen H, Sidtis JJ, Wesnes K *et al.* Effects of acute lorazepam administration on aminergic activity in normal elderly subjects: relationship to performance effects and apolipoprotein genotype. *Neurochem Res* 2004; **29**:1391–1398.
17. Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med* 2003; **49**:177–182.
18. Yotsutsuji T, Saitoh O, Suzuki M, Hagino H, Mori K, Takahashi T *et al.* Quantification of lateral ventricular subdivisions in schizophrenia by high-resolution three-dimensional magnetic resonance imaging. *Psychiatry Res* 2003; **122**:1–12.
19. Braak H, Braak E. On areas of transition between entorhinal allocortex and temporal isocortex in the human brain. Normal morphology and lamina-specific pathology in Alzheimer's disease. *Acta Neuropathol (Berl)* 1985; **68**:325–332.
20. Hanyu H, Shindo H, Kakizaki D, Abe K, Iwamoto T, Takasaki M. Increased water diffusion in cerebral white matter in Alzheimer's disease. *Gerontology* 1997; **43**:343–351.
21. Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, Virta A *et al.* Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage* 2001; **13**:1174–1185.
22. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Demyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 2002; **17**:1429–1436.
23. Roher AE, Weiss N, Kokjohn TA, Kuo YM, Kalback W, Anthony J *et al.* Increased A beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. *Biochemistry* 2002; **41**:11080–11090.
24. Song SK, Kim JH, Lin SJ, Brendza RP, Holtzman DM. Diffusion tensor imaging detects age-dependent white matter changes in a transgenic mouse model with amyloid deposition. *Neurobiol Dis* 2004; **15**:640–647.
25. Geroldi C, Pihlajamaki M, Laakso MP, DeCarli C, Beltramello A, Bianchetti A *et al.* APOE-epsilon 4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology* 1999; **53**:1825–1832.

Acknowledgement: J.N. is supported by a New Investigator Award from the Alzheimer's Association and N.P. by a grant from the National Institute of Mental Health (R01MH056994).