Title

P3-091 Regional distribution of white matter changes in Alzheimer's disease

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mechanism of contrast at 3 Tesla. T2 was measured with a whole-brain spin echo prepared 3D fast spin echo sequence using echo times of 16 and 76 ms. Thirteen subjects with AD (mean age 76, mean MMSE 19) and 11 age-matched control subjects (mean age 73) were studied. Images of the ratio of the short and long echo time were transformed to a standard space using SPM 99 software and compared for significant differences between patients and controls on a voxel by voxel basis. **Results:** Shortened T2 indicating elevated ferritin iron concentration was found in Alzheimer's patients in a bilateral distribution in the inferior putamen, globus pallidus and internal capsule. (Figure 1) Iron related changes were not seen in most of the cortex, perhaps due to masking from high T2 signal of CSF in areas of atrophy, though indications of shortened T2 were also seen in the posterior cingulate cortex. **Conclusions:** High field MRI can readily demonstrate differences in iron sensitive relaxation at high field strength in patients with Alzheimer's disease. High field MRI may be useful for longitudinal measurements to monitor the biochemical efficacy of metal chelation therapy. The spatial distribution of the iron related differences in AD encompasses the nucleus basalis of Meynert and may parallel the loss of cortical cholinergic enervation.

P3-089 A COVARIANCE RESTING PET PATTERN THAT DISCRIMINATES BETWEEN HEALTHY ELDERLY AND EARLY AD PATIENTS CORRELATES WITH FUNCTIONAL AND COGNITIVE SEVERITY IN SUBJECTS WITH COGNITIVE IMPAIRMENT BUT NO DEMENTIA

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Background: Multivariate techniques capture a different dimension of the imaging data (covariance among brain regions) than voxel-based or ROI analyses, but have rarely been used to in detecting AD. **Objective(s):** We sought to identify a single covariance pattern of relative rest blood flow that would help in discriminating between AD patients and elderly controls, and would display meaningful associations with cognitive performance measures in subjects with minimal to mild cognitive impairment (CI) but not dementia. **Methods:** Non-quantitative $H_2{}^{15}O$ PET scans during rest were acquired in 16 probable AD subjects selected for mild severity (modified Mini Mental Status examination [mMMS] 46/57; sd 5.1) (CDR = 1), 16 cognitively intact elderly controls (mMMS 54/57; sd 2.5) (CDR = 0) and 23 CI subjects (mMMS 54/57; sd 2.6) (broadly defined, including subjects with CDR = 0 and CDR = 0.5). AD-Control discrimination was attempted via (i) voxel-wise comparisons, (ii) ROI analyses and (iii) multivariate voxel-wise regional covariance analysis. The covariance analysis derived pattern was then prospectively applied to the CI subjects. **Results:** There were no significant mean flow differences in either voxel-wise or ROI analyses. However, the multivariate analyses identified a covariance pattern whose mean expression was significantly higher in the AD patients as compared to controls ($p = 0.03$) (sensitivity 76–94%; specificity 63–81%). Sites of increased concomitant flow included insula, cuneus, pulvinar, lingual, fusiform, superior occipital and parahippocampal gyri, whereas decreased concomitant flow was found in cingulate, inferior parietal lobule, middle and inferior frontal, supramarginal and precentral gyri. When prospectively applied to the CI subjects, the covariance pattern discriminated well between subjects with CDR = 0 and CDR = 0.5 ($p = 0.009$). Expression of this pattern correlated inversely with Selective Reminding Test total recall ($r = -0.401$, $p = 0.002$), delayed recall ($r = -0.351$, $p = 0.008$) and mMMS scores ($r = -0.401$, $p = 0.002$) in all 3 groups combined, and in the CI group alone. **Conclusions:** Multivariate techniques may be of use in early AD diagnosis even when univariate methods fail. They also provide a sensitive tool for differentiating subjects with CI into those with higher and lower functional and cognitive abilities, and perhaps into those with greater probability of subsequent conversion to AD.

P3-090 MRI SIGNAL HYPERINTENSITIES PREDICT MORE RAPID COGNITIVE DECLINE IN ALZHEIMER'S DISEASE (AD)

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Background: Cerebrovascular disease is common in the elderly, with or without AD. MRI frequently shows signal hyperintensities, of presumed microvascular origin, even in persons without clinical strokes. However, it is not established whether there is a relationship between onset, or course, of AD and these hyperintensities. **Objective:** Determine whether burden of MRI T2-weighted signal hyperintensities relates to rapidity of cognitive decline in AD. **Methods:** We used data from a longitudinal, three-site study of patients with mild AD who were followed with neuropsychological testing including modified Mini-Mental State (mMMS; scale 0–57) every 6 months, for an average followup period of 2.3 years. Entry criteria excluded patients with cortical infarcts or lacunes > 1cm. MRI films at baseline were available for 54 patients with mean age 75 yrs, education 14.9 yrs, and mMMS 43; this sample included 55% females, 56% apolipoproteinE4+, and 31% with hypertension, 12% diabetes, 18% hyperlipidemia, and 14% coronary heart disease. Each baseline FLAIR or T2-weighted MRI was rated, blind to clinical data, using the Scheltens scale (0–84 maximum) which includes assessment of periventricular, supratentorial, basal ganglionic, and infratentorial signal hyperintensities. **Results:** Mean Scheltens total score was 8.3. Average decline in mMMS was 3.26 points/year. Using GEE analysis, we found a significant relationship ($p = 0.04$) between Scheltens MRI score and the rate of cognitive decline: 0.13 mMMS points/Scheltens point/year, or about 5% increased speed of decline per Scheltens point. This relationship remained significant, even with adjustments for baseline mMMS, age, sex, education, and apoE4. Examination of Scheltens component scores showed that supratentorial white matter lesions were most responsible for the observed association ($p = 0.001$). The effect of white matter abnormalities was not simply related to vascular risk factors (hypertension, diabetes, hyperlipidemia, or heart disease), since even after further adjustment for these variables, the association of cognitive decline and MRI findings was preserved. **Conclusions:** Brain white matter signal change is associated with increased rapidity of cognitive decline in AD. This association does not appear to simply relate to underlying vascular risk factors, but may be due to white matter hyperintensities providing a superimposed injurious factor on AD pathology, contributing to cognitive decline.

P3-091 REGIONAL DISTRIBUTION OF WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE

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Background: While previous work in Alzheimer's Disease (AD) has carefully described gray matter changes, significant white matter (WM) volume loss and increases in abnormal signal in the WM have also been reported (e.g., Englund et al., 1987; Jernigan et al., 1991). Recent work has heightened interest in better understanding WM changes in AD. Bartzokis (2004) proposed a model of AD-related neurodegeneration based on the normal pattern of myelination; later-myelinating regions (e.g., temporal and frontal cortices) may be affected first in AD, relative to early-myelinating regions (e.g., primary motor cortex). There is a clear need for more information on regional WM changes across the lifespan and in AD (Jernigan et al., 2004). **Objective:** To systematically investigate the regional distribution of WM changes in AD with morphometric analyses of structural magnetic resonance imaging (MRI). **Methods:** Forty-eight AD and 44 elderly control (NC) participants were studied. Trained anatomists delineated frontal, parietal, occipital, temporal, and deep cerebral WM boundaries on tissue-segmented images. Regional WM volumes and amount of abnormal WM were mea-

sured. Regression and Mann-Whitney comparisons were used to determine group differences on volumes proportionalized to supratentorial cranial vault. **Results:** Along with significant gray matter loss, AD participants had less WM relative to NC participants, with an increase in the amount of abnormal WM (*Table*). All regional WM volumes were smaller in AD, although deep WM was not significantly smaller ($p = 0.10$). Temporal WM occupied a significantly smaller proportion of overall WM in AD relative to NC; deep WM occupied a significantly greater proportion. The significantly greater proportion of abnormal WM appeared to be distributed throughout the cerebrum, although it was disproportionately lower in the temporal region.

Table 1. Percent difference in median volume (md) of AD relative to NC group [(1 - ADmd/NCmd) × 100]

Region	WM Volume (%)	Abnormal WM Volume (%)
Total Cerebrum	−10.9	+48.1
Frontal Lobe	−12.0	+71.4
Parietal Lobe	−6.6	+52.2
Occipital Lobe	−8.6	+60.5
Temporal Lobe	−16.0	+16.4
Deep Region	−3.2	+25.5

Conclusions: AD participants had disproportionately less temporal WM, whereas deep WM was relatively spared. These preliminary regional findings lend support to the theory that the breakdown in AD is related to the pattern of myelination, although the findings related to abnormal WM changes are less clear. Future studies will examine the relationship of such structural changes to other measures of WM integrity and to the progression of AD. *Support: NIH/NIA P50AG05131, AG12674, & AG04085, DVA Medical Research Service*

P3-092 TEMPORAL LOBE GRAY MATTER REDUCTIONS IN ALZHEIMER'S DISEASE USING VOXEL-BASED MORPHOMETRY

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Background: Voxel-based morphometry (VBM) may afford a more rapid and extensive survey of structural abnormalities in Alzeheimer's disease than manually drawn resgion of interest analysis **Objective(s):** We used statistical parametric mapping to analyze magnetic resonance imaging scans from 18 AD patients and 16 normal comparison subjects. **Methods:** High spatial resolution structural images were normalized to the SPM99 template and then segmented, smoothed, and subjected to an ANCOVA. **Results:** The AD patients showed gray matter reduction in the anterior temporal cortex and the amygdala/antereior hippocampal region bilaterally. **Conclusions:** These results confirm previous findings of temporal lobe antrophic changes in AD.

P3-093 STRUCTURAL CORRELATES OF MILD COGNITIVE IMPAIRMENT

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Background: Hippocampal atrophy is the most frequently reported structural finding in mild cognitive impairment and early Alzheimer's disease. The contribution of other factors, such as cerebrovascular lesions, global brain atrophy, and estimates of premorbid brain volume is less clearly understood. **Objective(s):** To study the structural correlates of mild cognitive impairment. **Methods:** 105 elderly subjects whose cognitive function ranged from intact to demented, including 38 subjects with mild cognitive impairment (MCI). Hippocampal volumes (left and right HcV), brain volume (BV), and grey (GMV) and white matter volumes (WMV) were segmented from high resolution magnetic resonance data sets and normalised to intracranial volume (ICV). **Results:** Hippocampal volume reductions, but not global brain, white or grey matter atrophy, were associated with MCI. White matter lesion severity did not differ over cognitive states. In multivariate logistic regression models, normalised HcV and ICV were significant predictors of MCI versus normality. Normalised BV and ICV significantly predicted dementia versus MCI. Absolute volumetric measures yielded comparable classification accuracies. **Conclusions:** Hippocampal atrophy may be the crucial step for the transition from normality to MCI. Widespread brain atrophy may be the step to determine the transition from MCI to dementia. Brain volume reserve effects appear to be involved in both of these steps.

P3-094 PREDICTING COGNITIVE DECLINE WITH BASELINE HIPPOCAMPAL VOLUME AND RATE OF HIPPOCAMPAL ATROPHY

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Background: Because the hippocampus, a central structure for normal memory function, is an early site of Alzheimer's disease (AD), hippocampal volume at baseline or rate of volume change may predict subsequent cognitive decline. **Objectives:** To determine the extent to which hippocampal baseline volume or atrophy rate are related to cognitive decline in cognitively normal (CN) and mild cognitively impaired (MCI) subjects. **Methods:** Seventy-one CN and 39 MCI subjects were studied longitudinally with interscan period of 2.6 ± 1.2 years. CN subjects had cognitive dementia rating (CDR) scores of zero. MCI subjects had CDR of 0.5. Eleven CN and 12 MCI subjects, whose CDR scores increased at the time of their second MRI, were classified as cognitive decliners. Thirteen CN and 19 MCI had subcortical lacunes at first MRI. Hippocampal volume was measured on T1-weighted MRI. Logistic regression and receiver operator characteristics (ROC) were used to predict cognitive decline. **Results:** Decliners had smaller hippocampal volumes at baseline ($F(1,100) = 14.5$, $p < 0.001$) than non-decliners, after accounting for group, presence of subcortical lacunes, age and sex. Furthermore, decliners had higher rates of hippocampal atrophy ($F(1,100) = 46.9$, $p < 0.001$) than non-decliners, after accounting for group, presence of subcortical lacunes, age and sex. As expected, high rates of hippocampal atrophy were inversely correlated with small baseline volumes ($r = -0.48$, $p < 0.001$). Using baseline volume yielded a 79% overall classification and an area under ROC curve of 0.70 between decliner and non-decliner. Using atrophy rate yielded an 82% overall classification and an area under ROC curve of 0.82 between decliner and non-decliner. Furthermore, atrophy rate was significantly better ($p < 0.001$) than baseline volume in differentiating between decliner and non-decliner. **Conclusions:** Although atrophy rate and baseline volume of hippocampus are correlated, atrophy rate is better than baseline volume in predicting cognitive decline.

P3-095 AGE-DEPENDENT CHANGES IN REGIONAL BRAIN VOLUME AND CEREBRAL BLOOD VOLUME IN WHITE MATTER OF THE CANINE BRAIN MEASURED USING DYNAMIC SUSCEPTIBILITY CONTRAST MRI

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Background: White matter abnormalities, common in dementia and normal aging, are associated with impaired learning, memory, and speed of