

tivity theory will be employed for their analysis. The long term objective is to determine whether an individual's capacity for compensatory atypical memory network activation is related to incidence of clinical dementia.

**Methods:** This study forms one arm of the LAPSES study, a population-based longitudinal investigation of psychiatric, cognitive, neurological and neuroimaging characteristics of individuals with early memory complaints. Our paradigm is a 3T fMRI delayed match-to-sample task focused on episodic and spatial memory retrieval, in which the number of active visuospatial elements which define 'easy', 'moderate' and 'hard' task difficulty conditions are matched across subjects in pretesting by application of 90%, 70% and 50% performance criteria, respectively. While the active visuospatial elements vary across task difficulty, the overall number of elements is held constant by employing 'filler' stimuli, thus matching the perceptual load within subjects across the experiment. Connectivity tools employed to characterize functionally active memory-dependent networks will include Principal Component Analysis and wavelet analysis. **Results:** Preliminary functional connectivity data from 10 individuals with early memory complaints will be presented, with a focus on differential network activation when undergoing tasks of contrasting difficulty level. **Conclusions:** The significance of differential network activation with respect to task gradient will be discussed in relation to clinical neuroscience and prognosis of dementia.

**P2-365** EFFECTS OF AGING ON WHOLE BRAIN GRAY AND WHITE MATTER VOLUMES AND HIPPOCAMPAL SUBFIELDS

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**Background:** Although memory is commonly affected in elderly healthy subjects, neuroimaging studies seeking for age related hippocampal volume loss have been controversial. One reason for this might be that the hippocampus is not homogenous but consists of histologically and functionally different subfields which might be differently affected by age. **Objectives:** 1. To test for global age related gray and white matter volume changes. 2. To test if hippocampal age effects are global or subfield specific. **Methods:** 45 cognitively normal controls (aged 21-85, mean  $54.5 \pm 17.4$ , m/f: 27/18) were studied on a 4T magnet with the following sequences: 1. Volumetric T1-weighted gradient echo MRI (MPRage) resolution  $1 \times 1 \times 1$  mm. 2. High resolution T2-weighted fast spin echo  $0.4 \times 0.5 \times 2$  mm resolution, angulated perpendicular to the long axis of the hippocampus. The MPRage was segmented into gray (GM) and white maps (WM) which were used for optimized voxel-based-morphometry (VBM) in SPM2. The entorhinal cortex (ERC), subiculum, CA1, CA2 and CA3/4/dentate-compound were marked on the high resolution image on 5 consecutive slices using anatomical landmarks. The influence of age, gender and total intracranial volume on hippocampal subfields was tested using linear regression and regionally unbiased tests for age related GM/WM reductions were performed using SPM2. **Results:** VBM showed age related GM reductions bilaterally in hippocampus, putamen, thalamus, cerebellum, operculum, anterior and posterior cingulate and parieto-occipital and frontal cortex while WM reductions were found in corona radiata, corpus callosum, and periventricular, temporal and frontal WM. Significant negative age effects were found for ERC ( $p > 0.005$ ) and CA1 ( $p < 0.00001$ ) and significant age and gender effects ( $p < 0.025$ ) for CA2 which was primarily driven by volume loss in men. Neither CA1 nor ERC volume loss were correlated with GM losses after correction for age effects. **Conclusion:** Healthy aging is associated with regionally restricted volume loss that involves cortical regions including ERC. In the hippocampus, age effects are restricted to specific subfields, notably CA1 while others, e.g. subiculum are less affected. This regionally distinct pattern of atrophic changes, particularly also in the hippocampus, may have diagnostic value for early detection of Alzheimer's disease.

**P2-366** AMYLOID DEPOSITION BEGINS IN THE STRIATUM OF PRESENILIN-1 MUTATION CARRIERS FROM TWO UNRELATED PEDIGREES

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**Background:** Postmortem pathological studies have provided a retrospective reconstruction of the natural history of amyloid deposition in Alzheimer's disease (AD). While these studies have been valuable, recently developed PET radiotracers such as Pittsburgh Compound-B (PIB) allow prospective natural history studies of amyloid deposition in living subjects. Although it is difficult to predict which cognitively normal elderly are destined for brain amyloid deposition, carriers of mutations in the presenilin-1 (PS1) gene are known with certainty to be destined for AD and the accompanying amyloid pathology. **Objective:** Determine the early stages of the natural history of amyloid deposition in carriers of PS-1 mutations causing autosomal dominant early-onset familial AD. **Methods:** Three asymptomatic (C410Y; 35, 37, 38 y/o) and three symptomatic (A426P; 43, 45, 49 y/o) carriers of PS1 mutations and unaffected siblings were evaluated at the University of Pittsburgh Alzheimer Disease Research Center. Two more asymptomatic carriers (C410Y; 42 & 45 y/o) were evaluated at MGH. PIB PET imaging (15mCi, 60-90min) was then performed (ECAT HR+). Logan graphical analysis was applied to estimate regional PIB retention (distribution volume, DV), normalized to a cerebellar reference region DV to yield DV ratios (DVRs). MRI was performed for co-registration and partial volume correction. **Results:** Siblings (without mutations) of PS-1 mutation carriers showed no abnormalities on PIB PET imaging. The three clinically symptomatic mutation carriers showed markedly disproportionate accumulation of PIB in the striatum, but several other cortical areas with high PIB retention in sporadic AD (particularly precuneus) showed moderately increased PIB retention. The asymptomatic PS1 mutation carriers <40 y/o showed PIB retention mainly limited to the caudate, putamen and some thalamic nuclei, but not globus pallidus. The older asymptomatic cases showed early deposition in precuneus and frontal cortex as well. **Conclusions:** Amyloid deposition driven by PS-1 mutations appears to begin in the striatum. This may be different from sporadic AD, in which deposition may begin in frontal and precuneus cortex, but this is currently not clear. After the initial asymptomatic striatal phase, amyloid deposition in PS-1 mutation carriers appears to progress in a more typical fashion just prior to emergence of clinical symptoms.

**P2-367** PROGRESSIVE CORTICAL THICKNESS DECLINE IN ALZHEIMER'S DISEASE

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**Background:** Thickness of the cerebral cortex is known to decline in AD. Moreover, as the disease progresses additional cortical structures become afflicted by the spread of neurofibrillary tangles. **Objective:** We hypothesized that disease progression could be quantified and patterns of longitudinal change between healthy aging and AD compared using automated cortical thickness analyses. **Methods:** T1-weighted MRIs obtained from 19 AD patients (10 follow-up scans), and 18 Healthy Controls (HC, 18

follow-ups), were analyzed. Each scan was corrected for intensity non-uniformity [1], linearly registered into stereotaxic space [2] and tissue classified [3]. Subsequently, the inner and outer cortical surfaces were extracted [4], cortical thickness between these surfaces was measured in native-space mm and blurred with a 20mm diffusion-smoothing kernel [5]. All 40,962 vertices across the entire cortex underwent mixed-model analysis testing for thickness differences by diagnosis and interactions between follow-up scan interval and diagnosis. Multiple comparisons were accounted for using a 5% False Discovery Rate threshold [6]. **Results:** Cortical thickness was significantly different between AD and HC subjects in the medial frontal lobes, the posterior superior temporal gyri, the anterior cingulates, and, most significantly, the medial temporal lobes. The AD cohort had significantly greater decline than the HCs in the inferior temporal gyrus, the anterior cingulate, the orbitofrontal cortices, and the superior temporal gyri. **Conclusion:** The results, especially in the medial temporal lobes, show a progression from medial to lateral with follow-up (see figure). There is a large base-line difference in cortical thickness in the entorhinal cortex (0.7mm), the decline with follow-up in the AD group is 0.2mm/year. Moving laterally to the inferior temporal gyrus, there is little group difference initially, but a 0.45mm/year decline in thickness in the AD group. This suggests that the areas involved earliest in the disease, such as the entorhinal cortex, will have already undergone the most significant thinning, whereas areas involved later will exhibit greater thinning at follow-up.

[1] Sled et al., IEEE TMI, 17(1), 1998.

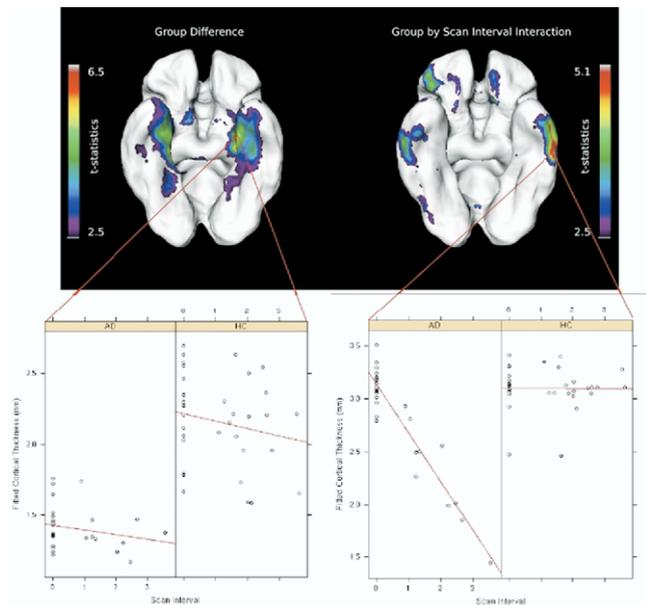
[2] Collins et al., JCAT, 18(2), 1994.

[3] Zijdenbos et al., IEEE TMI, 21(2), 2002.

[4] Kim et al., NeuroImage, 27(1), 2005.

[5] Chung et al., NeuroImage, 18(2), 2003.

[6] Genovese et al., NeuroImage, 15(4), 2002.



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#### ATROPHY IN THE PARIETOTEMPORAL REGIONS INCREASES THE RISK OF DEVELOPING ALZHEIMER'S DISEASE: A LONGITUDINAL MRI STUDY.

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**Background:** Neuropathology and structural imaging studies have established the involvement of the medial temporal lobe in Alzheimer's disease (AD). In contrast, the role of the posterior association areas is less well understood. Neuropathological analyses have described significant amyloid deposits in parietotemporal regions in the early stages of AD. Neuroimaging evidence from PET has, likewise, consistently shown abnormalities in the parietotemporal metabolism in AD. Structural abnormalities in this region have been difficult to quantify because identifying these cortices accurately on MRI has been methodologically challenging. Using procedures we recently developed (Fischl et al., 2004; Desikan et al, in press), we sought to determine whether progressive atrophy in the parietotemporal regions is evident on longitudinal MRI scans of subjects in the earliest stages of AD. **Methods:** 53 subjects (27 females) with SPGR scans at two time points (mean follow-up=2.74 years) were divided into two groups: subjects with normal cognition (CDR 0.0) at the time of both scans (n=23), and subjects with MCI (CDR 0.5) at the time of the first scan and had progressed to AD (CDR 1.0 - AD) at the time of the follow-up scan (n=30). The scans were processed, subdividing the parietotemporal region into 17 anatomically defined ROIs per hemisphere. Logistic regression analyses, controlling for intracranial volume and time between scans, were used to assess the relationship between the longitudinal change in volume of each region and the likelihood of being in the control or MCI/AD group. **Results:** Odds ratios were generated to determine when increased rates of atrophy posed significant risk for being in the MCI/AD group. The hippocampus and supramarginal gyrus showed the most significant elevations of risk (p's < 0.03) followed by the precuneus, banks of the superior temporal gyrus, inferior parietal lobule, fusiform gyrus, parahippocampal gyrus, inferior temporal gyrus and the middle temporal gyrus. **Conclusions:** These findings suggest that progressive atrophy can be identified and followed longitudinally in both parietotemporal and medial temporal regions during the prodromal phase of AD. They are consistent with neuropathological findings and functional imaging data that describe abnormalities in parietotemporal regions early in the course of AD.

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#### CORRELATION ANALYSIS OF THE HISTOFLUORESCENCE OF AN ANALOGUE OF PITTSBURGH COMPOUND-B AND A $\beta$ PEPTIDE LEVELS IN ALZHEIMER'S DISEASE

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**Background:** Evaluation of therapies designed to alter the progression of Alzheimer's disease (AD) can be facilitated by *in vivo* imaging of brain pathology. The PET radiotracer Pittsburgh Compound-B (PIB) is believed to bind selectively to amyloid deposits *in vivo*, due to its high binding affinity for the  $\beta$ -pleated sheet protein conformation. Abnormal amyloid conformation is common to all major neuropathological changes in AD brains, including amyloid- $\beta$  (A $\beta$ ) plaques, neurofibrillary tangles (NFT), dystrophic neurites (DN) and neuropil threads (NT). **Objective(s):** To provide histological validation for PIB binding *in vivo*, we recently undertook a detailed characterization of the binding of 6-CN-BTA-1 (6-CN), a highly fluorescent derivative of PIB, in post-mortem AD brain tissue, and demonstrated co-localization of 6-CN histochemistry with A $\beta$  plaques revealed by immunohistochemistry. We extended this study by examining the relationship of 6-CN labeled plaques with levels of soluble and insoluble A $\beta$ 1-40 and A $\beta$ 1-42. **Methods:** 6-CN histochemistry was performed on temporal cortex tissue sections from 9 AD patients diagnosed in the University of