P1-242 ALTERED HIPPOCAMPUS FUNCTIONAL CONNECTIVITY IN THE RECOGNITION MEMORY NETWORK CORRECTED FOR GREY MATTER ATROPHY IN MILD COGNITIVE IMPAIRMENT

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Background: Mild cognitive impairment (MCI) has been associated with increased risk to develop Alzheimer's disease (AD), with episodic memory impairment being of the earliest symptoms preceding dementia. Hippocampus has been shown to be involved in episodic memory and is altered in MCI. Recent studies have shown that functional connectivity[1] of hippocampus activity within a larger cortical default network is altered in MCI and AD. Here we investigated to what extent hippocampus functional connectivity as assessed during episodic memory retrieval is altered. Since hippocampus has been found to be reduced in MCI we investigated in addition to what extent grey matter volume changes may influence functional connectivity changes of hippocampus. **Methods:** Functional MRI was acquired during delayed forced-choice word recognition task in healthy controls (HC, n = 10) and MCI (n = 8) subjects. Hippocampus volume was manually outlined on T1 weighted volumetric MRI scans according to an established volumetric protocol and used as mask to extract the average positive hippocampus activity during trials of successful retrieval. Hippocampus connectivity was assessed voxel-based by regression of hippocampus volume onto brain activity in the rest of the brain voxel-by-voxel controlling for age and, optionally, hippocampus volume differences. **Results:** Functional hippocampus connectivity during a forced-choice visual verbal recognition memory task was found to be bilaterally dramatically reduced in spatial extent in MCI subjects when compared to HC. HC showed increased hippocampus connectivity within large-scale neuronal network including prefrontal, lateral temporal, posterior parietal, occipital, cerebellar brain areas. Notably, whereas HC showed only positive hippocampus correlations, MCI patients showed only negative hippocampus correlations primarily confined to medial and anterior prefrontal cortex. Hippocampus connectivity in MCI within right dorso-lateral prefrontal cortex and middle anterior cingulate gyrus was no longer different from HC when hippocampus volume was controlled for. **Conclusions:** The current findings show that hippocampus related network is markedly altered in MCI, partially dependent upon hippocampus volume deficits, that may underly episodic memory deficits in MCI.

References Bokde AL, Lopez-Bayo P, Meindl T, et al. Functional connectivity of the fusiform gyrus during a face-matching task in subjects with MCI. *Brain* 2006;129:1113-1124.

P1-243 QUANTIFYING METABOLIC ASYMMETRY IN ALZHEIMER'S DISEASE USING BOTH MR AND PET IMAGING

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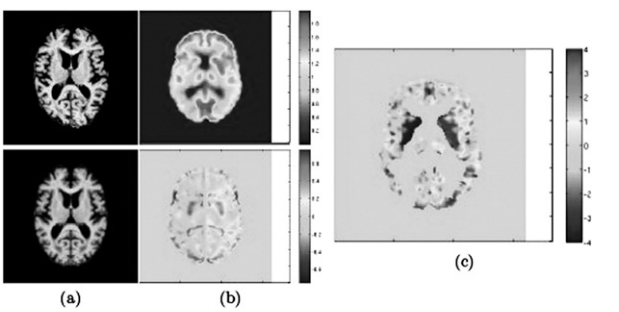
Background: Some of the earliest studies of FDG-PET in Alzheimer's disease (AD) noticed that patients sometimes had predominant left or right hemisphere hypometabolism. Currently, asymmetry in clinical brain scans is interpreted using only visual inspection. Quantifying metabolic asymmetry is difficult because mirroring values about the midsagittal plane does not necessarily align homologous structures in the left and right hemispheres. The objective of this research is to automatically quantify statistically significant areas of metabolic asymmetry in AD, while removing the confounding effects of structural asymmetry. **Methods:** We constructed an atlas of normative metabolic asymmetry from 10 normal control subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and quantified the metabolic asymmetry of an AD subject compared to the normative atlas. A symmetric structural image for each subject was computed using an unbiased average image from the original MRI and the MRI mirrored about the midsagittal plane. The PET image was mapped onto this structurally symmetric image, and an asymmetry image was computed as the difference of the left minus the right side. Since this is done in structurally symmetric coordinates, metabolism was compared across homologous structures of each hemisphere. Next, we built a structurally symmetric atlas of the 10 control subjects from an unbiased average of their symmetric MR images. The mean and standard deviation of the population's metabolic asymmetry was computed in the symmetric atlas coordinates. Finally, we registered the asymmetry image from an AD subject to the normal atlas and computed a pixel-by-pixel z-score of metabolic asymmetry. **Results:** Average normal asymmetry was in the range -0.15 to 0.15 relative to pons, with a maximal standard deviation of 0.35. The asymmetry z-score map of the AD patient shown in the figure showed significant ($z > 3$) asymmetry, which verifies and quantifies the asymmetry found by visual inspection. **Conclusions:** Structurally symmetric image coordinates are an effective approach to locating and quantifying asymmetry of glucose metabolism in AD. Acknowledgements: Supported in part by the Center for Alzheimer's Care, Imaging and Research and NIH grant AG024904.

References: Fletcher, et al., IPMI 2007, pp. 346-358.



Shown in (a) are original MRI scan (top) and the associated structurally symmetric image (bottom) of a subject with AD. Shown in (b) top is the subjects PET scan. Shown in the (b) bottom is the metabolic asymmetry image mapped in to the atlas space. Shown in (c) is the image of the statistical significance of metabolic asymmetry as compared to the normative atlas.

P1-244 FREQUENCY OF HEMISPHERIC METABOLIC ASYMMETRY IN PROBABLE ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) causes, on average, a symmetric pattern of glucose hypometabolism. However, some patients have hypometabolism predominantly affecting either the left or right hemisphere. These patients may have atypical presentations that could cause them to be systematically excluded from clinical drug trials. It is unknown whether the left or

right hemisphere is more likely to be selectively affected. Furthermore, the frequency of significant hemispheric metabolic asymmetry is unknown. **Methods:** We evaluated 95 baseline FDG-PET scans in patients with clinically diagnosed mild AD (MMSE 20-27) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Each scan was analyzed with Neurostat, providing 3D-stereotactic surface projection (3D-SSP) maps of glucose metabolism relative to pons and corresponding statistical maps of Z-scores computed in comparison to 27 cognitively normal elderly control subjects. We visually evaluated the pattern of glucose hypometabolism, considering 5 regions in each hemisphere typically affected in dementia. Hemispheric asymmetry was considered significant when hypometabolism was 2 or more standard deviations greater in one hemisphere. We also calculated 3D-SSP maps of mean rates of glucose metabolism and Z-score maps. **Results:** Ten patients had an FTD-like pattern of hypometabolism and were excluded from further analyses. In the remaining 85 AD subjects, FDG-PET images were symmetric in 70 (82.4%). Hypometabolism predominantly involved left hemisphere regions in 8 (9.4%) and predominantly involved right hemisphere regions in 7 (8.2%). These groups did not differ significantly in age or dementia severity as measured by MMSE. Impairment was greater in naming and word fluency for patients with predominant left hemisphere hypometabolism and clock drawing scores were lowest for those with predominant right hemisphere hypometabolism. **Conclusions:** Although AD patients as a group have completely symmetric glucose hypometabolism, individual patterns vary reflecting cognitive differences. In this sample, roughly similar proportions of left and right predominant hypometabolism was seen in a minority of patients. The frequency of metabolic asymmetry may differ in community samples. The mechanisms accounting for selective involvement of one hemisphere are unexplained and need to be explored further. Supported in part by the Center for Alzheimer's Care, Imaging and Research and NIH grant AG024904.

P1-245 MAPPING LOCAL STRUCTURAL HIPPOCAMPAL CHANGES IN ALZHEIMER'S DISEASE AND NORMAL AGING ON MR IMAGING AT 3T

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Background: Histological studies suggest that hippocampal subfields are differently affected by aging and Alzheimer's disease. We aimed to study local hippocampal changes in aging and moderate to severe Alzheimer's patients based on high resolution magnetic resonance images at 3 Tesla. **Methods:** 3D high resolution T1-weighted magnetic resonance (MR) were acquired on a 3.0 T scanner from 14 AD (age 75±5 years, 3 males, Mini Mental State Examination 13±4) and 14 controls (age 71±5 years 9 males, Mini-Mental State Examination 29±1). The hippocampal formation was isolated by manual tracing. Radial Atrophy Mapping was used to assess group differences and correlations by averaging hippocampal shapes across subjects using 3-dimensional parametric surface mesh models. Percentage difference, Pearson's *r*, and significance 3-dimensional maps were produced. **Results:** Hippocampal volumes were inversely correlated with age in older healthy controls (r= .53 and .56 to the right and left, p< 0,05, corresponding to 17% lower volume for every 10 years of older age from age 65). Aging-associated atrophy mapped to dorsal and lateral areas of the tail and body corresponding to the CA1 subfield and to ventral areas of the head corresponding to the subiculum. Significantly increased volume with older age mainly mapped to restricted dorsal areas of the head bilaterally corresponding to the CA1 subfield. Volumes were 37% and 30% smaller in AD patients to the right and left (p<.0005). AD-associated atrophy mapped to areas of the body and tail corresponding to those also associated with age, and dorsal areas of the head corresponding to the CA1 subfield unaffected by age. Regions corresponding to the CA2-3 fields were relatively spared in both aging and AD. **Conclusions:** Hippocampal atrophy in AD maps to areas in the body and tail partly overlapping to those affected by normal aging. Specific areas in the anterior and dorsal CA1 subfield involved in AD were not in normal aging. Such differences might relate to specific systems being involved in AD and ageing.

P1-246 WHITE MATTER HYPERINTENSITIES IN ALZHEIMER PATIENTS AND NON-DEMENTED ELDERLY: POSTMORTEM QUANTITATIVE MRI AND NEUROPATHOLOGICAL CHARACTERISTICS

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Background: The association between white matter hyperintensities (WMH) on conventional MRI and cognitive decline in Alzheimer's disease (AD) and in healthy elderly is only weak and inconsistent. A possible explanation for this would be heterogeneity in the neuropathological substrate underlying WMH. In vivo quantitative MRI techniques may improve the clinico-radiological association. We assessed whether postmortem quantitative MRI reflects differences in neuropathological correlates of WMH in AD and controls. **Methods:** Thirty-three formalin-fixed, coronal brain slices from 11 AD patients (mean age: 83 ± 10 yrs, 8 females) and 15 slices from 7 non-demented controls (mean age: 78 ± 10 yrs, 4 females) with WMH were scanned with qualitative (FLAIR) and quantitative MRI (diffusion tensor imaging [DTI] with b = 750 s/mm2, and T1-relaxation time mapping based on flip-angle array) using a 1.5T Siemens Vision scanner. 104 Regions of interest (ROIs) were defined on FLAIR images in WMH and normal appearing white matter (NAWM; 45 WMH and 30 NAWM ROIs in AD; 16 WMH and 13 NAWM ROIs in controls). Histopathological examination included (semi)-quantitative assessment of axonal density (Bodian), myelin density (LFB), astrogliosis (GFAP), microglial activation (LN3). **Results:** Overall, AD patients had a lower fractional anisotropy (FA) and a higher T1 than controls. WMH had lower FA and higher T1 values than NAWM in both groups. More specifically, WMH of AD patients differed from WMH of controls as it had lower FA and higher T1 values (unpaired T-test: mean FA = 0.44 ± 0.10 vs 0.57 ± 0.07, p= 0.001 and mean T1[ms] = 464 ± 83 vs 398 ± 98, p= 0.01; for AD vs controls). Within the group of AD patients, lower FA and higher T1 correlated with axonal and myelin loss and more microglial activation (Spearman's r: FA= -0.60, -0.41, -0.27 and T1= 0.61, 0.49, 0.38 for axonal density, myelin density and microglial activation, respectively; all p<0.001, except for the correlation between FA and microglial activation: p<0.05). **Conclusions:** Postmortem quantitative MRI (DTI, T1-mapping) reveals differences between WMH in AD and in non-demented elderly. Moreover, postmortem quantitative MRI reflects the severity of axonal and myelin loss and microglial activation.

P1-247 CLINICAL SEVER… IS ASS…

WITHDRAWN

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