Hippocampal Atrophy Patterns in Mild Cognitive Impairment and Alzheimer's Disease

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Background

Memory impairment is a characteristic early sign of Alzheimer's Disease (AD) and atrophy of the hippocampal formation is one of its earliest hallmarks. The hippocampus is not a homogeneous structure but consists of several subfields with distinct histological characteristics: the subiculum, the four cornu ammonis sectors (CA1-4) and the dentate gyrus. There is evidence from animal and histopathological studies that different disease processes affect subfields differently. Therefore, measurements of hippocampal subfield volumes might yield a better distinction between different disease processes and allow for an earlier diagnosis of diseases affecting the hippocampus than measurements of the total hippocampal volume. The specific aims of this study were the following: 1. To determine if patterns of volume loss in hippocampal subfields in patients suffering from AD and mild cognitive impairment (MCI) are different from normal aging. 2. To test if the measurement of hippocampal subfields allows for a better discrimination between controls and patients suffering from mild cognitive impairment or AD than measurements of total hippocampal volume loss.

Methods

75 subjects (47 cognitively intact controls, 14 subjects diagnosed with mild to moderate AD (mean MMSE 21.3 ± 5.7) and 14 subjects diagnosed with mild cognitive impairment (MCI) (MMSE 27.5 ± 2.1), mean age 70.0 ±.8.2, range: 56-84 years, female/male (f/m) 27/48) were studied on a Bruker MedSpec 4T system equipped with an eight channel phased-array receive coil. The following sequences were obtained: 1. Volumetric T1-weighted gradient echo MRI (MPRAGE) (TR/TE/TI = 2300/3/950 ms, 7^o flip angle, 1.0 x 1.0 x 1 mm^3 resolution). 2. High resolution T2 weighted fast spin echo sequence (TR/TE: 3500/19 ms, echo train length 15, 18.6 ms echo spacing, 160° flip angle, 0.4 x 0.5 mm in plane resolution, 2 mm slice thickness, 24 interleaved slices without gap, angulated perpendicular to the long axis of the hippocampus.). On the high resolution T2 weighted image the entorhinal cortex (ERC), subiculum, CA1, CA1-2 transition and CA3&dentate on both sides were marked on five consecutive slices using anatomical landmarks Total hippocampal volume was determined from the MPrage using the FreeSurfer software parcellation routine (1). Multiple linear regression analyses were used to identify volumes with significant disease state effects and then further explored using one-way ANOVA tests .To identify the subfield volumes which distinguished best between disease groups, a stepwise linear discriminant analysis and power analyses were performed

Results

Multiple regression analysis showed significant effects for disease state for ERC (p=0.0057), subiculum (p=0.0015), CA1 (p<0.0001), CA1-2 transition (p<0.0001) and total hippocampal volume (p=0.0005) but not for CA3&DG. Post hoc analyses showed that subjects suffering from AD had significantly reduced ERC subiculum, CA1, CA1-2 transition and total hippocampal volumes whereas CA3&DG volumes were not different when compared to controls. Subjects diagnosed with MCI showed significant volume losses in CA1 and CA1-2 transition but not in ERC, subiculum or CA3&DG when compared to controls (cf. Table 1). There were no significant differences between AD and MCI. Stepwise linear discriminant analysis showed that CA1-2 transition distinguished best between AD and controls (Wilks' Lambda 0.72, p<0.0003, 16.4% misclassified, 1 AD, 9 controls); CA1-2 transition also discriminated best between MCI subjects and controls (Wilks' Lambda 0.68, p<0.0001, 16.4 % misclassified, 2 MCI, 8 controls).. Power analysis showed that the power to detect a difference between subjects diagnosed with AD and controls, respectively subjects diagnosed with MCI and controls at the significance level alpha = 0.05 was 0.93, respectively 0.55 for ERC; 0.97, respectively 0.28 for subiculum; 0.99, respectively 0.90 for CA1 and 0.98, respectively 0.92 for CA1-2 transition. For the hippocampus, the power was 0.98, respectively 0.32.

	Control N = 47	MCI N = 14	AD N = 14
ERC	202.4 ± 54.0	168.4 ± 48.0	145.0 ± 53.4*
Subiculum	200.2 ± 36.1	184.7 ± 38.1	154.2 ± 44.9*
CA1	331.4 ± 47.0	285.1 ± 42.5*	264.4 ± 63.1*
CA1-2 transition	20.5 ± 5.5	15.1 ± 3.4 *	14.1 ± 3.8*
CA3&DG	224.4 ± 37.7	227.2 ± 24.3	230.3 ± 54.7
Total Hippocampus	5520.6 ± 770.4	5154.9 ± 817.7	4450.8± 1285.2*

Table 1: Subfield and Total Hippocampal volumes in mm3

Conclusions

Hippocampal volume loss in the AD is not diffuse but regionally selective. In AD the most prominent volume losses were found in CA1-2 transition, CA1, subiculum and ERC but were restricted to CA1 and in CA1-2 transition in MCI. In the latter region, the volumes loss was of similar magnitude as in subjects with AD. This distribution of hippocampal volume loss in AD is clearly different from the distribution found in normal aging which is most pronounced in CA1 but does not affect CA1-2 transition and subiculum (2) and closely resembles the pattern of neuron loss described in histopathological studies of AD and MCI. Volume loss in the dorsal medial aspect of the hippocampus (CA1-2 transition zone) was shown to be a good measure to distinguish between subjects suffering from MCI and controls and between subjects diagnosed with AD and controls. The power analyses showed that CA1-2 transition zone and total hippocampal volume did equally well in distinguishing between AD and controls, but that CA1-2 transition zone was clearly superior to total hippocampal volume in distinguishing between MCI and controls. This suggests that subfield measurements might be a more sensitive way to detect early AD than measurements of the whole hippocampus but provide no additional information in more advanced stages of the disease.

References: 1. Fischl B et al. Neuron 2002; 33: 341-355 2. Mueller SG et al. Neurobiol Aging 2007; 28: 719-726