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Increased hippocampal head diffusivity predicts impaired episodic memory performance in early Alzheimer's disease

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ABSTRACT

Recent neuroanatomical and functional neuroimaging studies indicate that the anterior part of the hippocampus, rather than the whole structure, may be specifically involved in episodic memory. In the present work, we examined whether anterior structural measurements are superior to other regional or global measurements in mapping functionally relevant degenerative alterations of the hippocampus in Alzheimer's disease (AD).

Twenty patients with early AD (MMSE 25.7 ± 1.7) and 18 healthy controls were studied using magnetic resonance and diffusion-tensor imaging. Using a regions-of-interest analysis, we obtained volumetric and diffusivity measures of the hippocampal head and body-tail-section as well as of the whole hippocampus. Detailed cognitive evaluation was based on the CERAD battery.

All volumetric measures as well as diffusivity of the hippocampus head were significantly ($p < 0.01$) altered in patients as compared to controls. In patients, increased left head diffusivity significantly ($p < 0.01$) correlated with performance on free delayed verbal recall test (DVR) ($r = -0.74$, $p = 0.0002$) and with the CERAD global score. Reduced volume of the left body-tail was also associated with performance on DVR ($r = 0.62$, $p = 0.004$). Stepwise regression analyses revealed that increased left head diffusivity was the only predictor for performance on DVR ($R^2 = 52\%$, $p < 0.0005$).

These findings suggest that anterior hippocampus diffusivity is more closely related to verbal episodic memory impairment than other regional or global structural measures. Our data support the hypothesis of functional differentiation in general and the specific role of the anterior hippocampus in episodic memory in particular. Diffusivity measurements might be highly sensitive to functionally relevant degenerative alterations of the hippocampus.

1. Introduction

There is strong empirical evidence that the hippocampus plays a crucial role in encoding and retrieving new memories (Squire, 1992). Yet, functional specialization within the hippocampus remains controversial. To explain hippocampal function in relation to the cytoarchitectural divisions, more attention has focused on the horizontal axis than on the longitudinal axis of the hippocampal formation. During the last 15 years, however, it has become clear that functional specialization along the longitudinal axis is fundamental to hippocampal function. This evidence has come primarily from lesion experiments on animals (Moser, Moser, & Andersen, 1993; Moser, Moser, Forrest, Andersen, & Morris, 1995), but it has rapidly been supported by functional neuroimaging studies in human (see Schacter & Wagner, 1999 for review and references). More specifically, functional magnetic resonance imaging (fMRI) findings indicated a relationship between the anterior part of the hippocampus and associative memory. Recently, Chua, Schacter, Rand-Giovannetti, and Sperling (2007) highlighted a specific role of the anterior hippocampal formation in successful memory encoding.

The hippocampal formation is the first brain structure to be affected by Alzheimer's disease (AD) (Braak & Braak, 1991) and, correspondingly, prospective studies have found that memory

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deficits are the first clinical signs of AD (Jacobs et al., 1995). Therefore, this limbic area has been the focus of special research attention. AD-associated pathological alterations of the hippocampus at very early stages of the disease have been systematically demonstrated using various neuroscience techniques. Among neuroimaging methods, MRI-based hippocampal volumetry is likely to be the most widespread diagnostic tool (de Leon et al., 2007). Generally, regional cerebral volume reduction is regarded to reflect neuronal cell loss. Accordingly, total numbers of neurons in the hippocampus strongly correlate with MRI-determined hippocampal volume in AD (Bobinski et al., 2000). Numerous studies have consistently demonstrated hippocampal atrophy not only in patients with very mild AD, but also in subjects with mild cognitive impairment (MCI) whose cognitive deficits are limited to the memory domain (i.e., amnestic MCI, aMCI) (Convit et al., 1997; Wolf et al., 2001). Furthermore, hippocampal size reduction predicted conversion to AD in aMCI and in normal elderly (Jack et al., 2005; Wolf et al., 2003).

While a critical role of hippocampal atrophy in early diagnosis of AD is apparent, fewer consistencies exist in respect of its functional implications. The association between hippocampal volume and episodic memory performance (as assessed by free delayed verbal recall test, DVR) is controversial. Presence (e.g., Devanand et al., 2007; Laakso, Hallikainen, Hänninen, Partanen, & Soininen, 2000) as well as absence (e.g., Basso et al., 2006; Walhovd et al., in press) of a (positive) correlation has been reported in AD and aMCI. Notably, within one study paradigm, Fjell et al. (2008) found a positive association between the hippocampal volume and performance on DVR in one MCI sample, but not in another. This suggests that the situation is complex and factors beyond methodological differences (e.g., vascular, hormonal) (Geuze, Vermetten, & Bremner, 2005) may account for the variability in volumetric measurements in general and their relationship with memory in particular. Overall, the existing evidence indicates that hippocampal atrophy might not be an ideal marker of hippocampus dysfunction.

Diffusion-tensor imaging (DTI) measures the random, unidirectional motion of water molecule protons in biologic tissue (Le Bihan et al., 2001). The mean diffusivity (MD) is a measure of randomized mean water diffusion. As any neurodegenerative process is accompanied by a progressive loss of barriers that restrict water molecule motion (e.g. neuronal loss), it can be sensitively detected by DTI as pathologically elevated MD (Beaulieu, 2002). Accordingly, early DTI studies documented increased MD in hippocampal regions of patients with AD and aMCI (Fellgiebel, Wille, et al., 2004; Kantarci et al., 2001). Later our group showed that increased hippocampal diffusivity was associated with impaired verbal memory performance in aMCI (Müller et al., 2005). Furthermore, Kantarci et al. (2005) and Fellgiebel et al. (2006) found that hippocampal diffusivity was superior to hippocampal volume measurements in predicting conversion of aMCI to dementia.

In the present study, we examined whether anterior hippocampal diffusivity or volume measurements are superior to global or posterior measurements in mapping functionally relevant degenerative alterations of the hippocampus in early AD. Guided by the concept of functional differentiation, we hypothesized that AD-associated increased hippocampal head diffusivity would be a more sensitive marker of episodic memory impairment than other regional or global diffusivity or volumetric measurements.

2. Methods

2.1. Subjects and design

The local ethics committee approved the study and written informed consent was obtained from all participants. Subjects with early AD were identified from the database of patients referred to the memory clinic of the Department of Psychiatry of the University of Mainz. This database was searched for subjects who, in addition to the diagnostic routine, have undergone an MRI examination according to the protocol described below. Diagnostic procedures comprised clinical psychiatric and neurological examinations, cranial MRI, [(18)F]fluorodeoxyglucose (FDG) positron emission tomography (PET), and laboratory tests including thyroid hormones, vitamin B12 and folate.

Table 1
Demographic characteristics.

	Early AD	Controls	p (t-test)
N (female)	20 (4)	18 (7)	n.s.[a]
Age, years	69.8 ± 7.4	69.0 ± 6.7	n.s.
Education, years	13.3 ± 2.1	13.6 ± 3.0	n.s.
MMSE	25.7 ± 1.7	28.9 ± 1.0	<0.001

Data are presented as mean ± standard deviation. MMSE = Mini-Mental State Examination; n.s. = not significant.

[a] Chi-square test.

Early AD was defined as a history of progressive cognitive decline over at least 6 months with memory impairment, a Clinical Dementia Rating (CDR; Morris, 1993) of 0.5 or 1.0, and a score on the Mini-Mental State Examination (MMSE) of at least 23 points. In the absence of a histopathological confirmation of AD, we utilized an "Alzheimer-typical" finding on FDG-PET (Fellgiebel, Siessmeier, et al., 2004; Yakushev et al., 2008) as additional biological marker (Dubois et al., 2007). In this situation, a "positive" PET scan (i.e. a typical pattern of hypometabolism) has been shown to increase the probability of AD pathology to 84% (Jagust, Reed, Mungas, Ellis, & Decarli, 2007). Exclusion criteria were a history or presence of other organic brain diseases, substance abuse, all psychiatric diagnoses other than dementia (including major depression), diabetes mellitus, and evidence of leucoencephalopathy on T2- and FLAIR-weighted MR images. By these criteria, twenty right-handed patients, 15 with CDR 0.5 and 5 with CDR 1.0, were included in the study.

Eighteen control subjects were recruited by advertisement and comprised healthy elderly right-handed individuals without cognitive impairment, without clinical evidence of any neurologic, medical, or psychiatric condition that could affect cognition, and normal MRI findings on visual inspection. Demographic characteristics of patients and controls are given in Table 1.

Cognitive evaluation of all participants was based on the German version of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) battery (Welsh et al., 1994). Raw scores on each test were converted to standardized scores (z-scores) using the population mean and standard deviation, adjusted for age, sex, and education (Welsh et al., 1994).

2.2. MR data acquisition

MRI examinations were performed within a few days of the clinical and neuropsychological exams. All data were obtained on a 1.5 T system with gradients of 40 mT/m (Magnetom Sonata, Siemens). Apart from the acquisition of routine T1-weighted (TR/TE: 600 ms/25 ms, Matrix 256 × 256), PD/T2-weighted (TR/TE1/TE2: 4500 ms/15 ms, 100 ms, Matrix 256 × 256), FLAIR (TR/TE 9000 ms/108 ms, slice thickness 6 mm, Matrix 512 × 448) images and 3D-MP RAGE (TR/TE: 1900 ms/16 ms, Matrix 512 × 512) data sets with a 1 mm^3 isotropic voxel size, we used a transversal diffusion-weighted single-shot spin–echo echo-planar (EPI) based sequence with gradients along 6 non-collinear directions (TR/TE = 8000/105 ms, b = 0 and 1000 s/mm^2, matrix 128 × 128, slice thickness 3 mm without gap (voxel size 1.8 mm × 1.8 mm × 3.0 mm) and 6 averages. All transversal slices were arranged parallel to the AC-PC line (anterior–posterior commissure). Scans showing severe motion artefacts were excluded.

2.3. DTI data postprocessing

Diffusion tensors (D) were computed by fitting the model described in Basser, Mattiello, and Le Bihan (1994) to the signal intensities measured with the above-mentioned DTI imaging sequence. The decomposition of D into its eigenvalues (λ_1, λ_2, λ_3) and eigenvectors (ε_1, ε_2, ε_3) was accomplished by symmetric bi-diagonalization followed by QR-reduction routines as implemented in GSL (GNU Scientific Library version 1.13 http://www.gnu.org/software/gsl). MD was calculated as the mean of the eigenvalues of the diffusion tensor [$(\lambda_1 + \lambda_2 + \lambda_3)/3$] and is given in mm^2/s [2]. The indices were plotted voxel by voxel as MD index maps.

2.4. Hippocampal volumetry

Except for coregistration, all subsequent operations were performed using Analyze® Software (Version 8.1; Biomedical Imaging Software System, Mayo Foundation for medical education and research, Rochester). The operator manually traced the hippocampus boundaries slice-by-slice according to a standardized protocol (Niemann, Hammers, Coenen, Thron, & Klosterkotter, 2000). The intraplane hippocampal boundaries were defined to include the CA1 through CA 4 sectors of the hippocampus proper, the dentate gyrus and the subiculum. The border between the anterior part of the hippocampus (=hippocampal head) and the posterior body-tail-