Does the Hippocampal Atrophy Correlate With the Cortical Theta Power in Elderly Subjects With a Range of Cognitive Impairment?

Martin Grunwald, Anke Hensel,† Henrike Wolf,† Thomas Weiss,‡ and Hermann-Josef Gertz†*

Summary: A previous study with a small sample (N = 39) showed a significant correlation between the cortical theta activity and the hippocampal volume in different stages of cognitive impairment in aged subjects. The recent study was aimed to replicate these results in a much bigger sample. The authors examined a sample of 121 right-handed subjects. The sample consisted of 37 healthy controls, 40 patients with questionable dementia, and 44 patients with mild dementia assessed by Clinical Dementia Rating. All subjects underwent EEG and brain MRI. Mean spectral power was calculated, and volume of hippocampal segments was measured. EEG theta power of the left and right hemisphere correlated significantly with the hippocampal volume on the left and right side in different stages of cognitive impairment. An increase of theta power was associated with decreased hippocampal volume. No other significant correlations were found for alpha or beta band power. No correlation was found between cortical theta and global brain volume. There seems to be a direct relationship between neuronal loss of the hippocampus and changed cortical theta activity for different stages of cognitive impairment in aged subjects.

Key Words: Cortical theta, EEG, Hippocampus, Mild cognitive impairment, Mild dementia.

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Increased brain electrical theta activity and a decrease of hippocampal volume described two relevant parameters that discriminate patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy controls (CO) (Förstl et al., 1996; Prichep et al., 1994). Functional relations seem to exist between cortical theta activity and the hippocampus (Miller 1991; Vinogradova 1995). A high correlation between theta activity and an excessive neuronal loss in the hippocampi was found at autopsy in AD patients (Rae–Grant et al., 1987). Therefore, it can be presumed that a neuronal loss in the hippocampus may lead to changes in the slow-wave theta activity of the neocortex.

It was demonstrated in 39 subjects that the cortical spectral power density of the theta frequency band (4–8 Hz) within the EEG (theta power) under rest condition (eyes closed) is negatively correlated with the volume of the hippocampus in subjects with different degrees of cognitive impairment (MCI, CO, mild dementia). Such a negative correlation was found only for the theta power and not for other bands of the EEG spectra (Grunwald et al., 2001).

The aim of the present study was to replicate this examination in a bigger sample size of patients. According to the first study, we tested the hypothesis that a decrease of hippocampal volumes correlates negatively with an increase of cortical theta power over frontal regions under rest conditions (eyes closed). No correlations were expected for all other EEG bands. We also expect that the theta activity correlates specifically with the hippocampal volume and is not relative to the global brain volume.

METHODS

Participants

A total of 121 participants within aged 52 to 90 years were enrolled. Patients without dementia symptoms (53%) were recruited for this study from the Leipzig Longitudinal Study of the Aged (LEILA 75+) (Riedel–Heller et al. 2001). The remaining participants were recruited from referrals to the local memory clinic. To ensure that participants represented a cognitive continuum, they were recruited according to Mini-Mental State Examination strata (for more details see Wolf et al., 2004). Exclusion criteria were physical and/or neurologic disabilities (such as blindness, deafness, severe movement disorders or paralysis) that would have interfered with the subject's ability to complete neuropsychological tests or paraclinical examinations (such as computed tomography, EEG or MRI procedures).

All subjects were clinically assessed as described previously (Wolf et al., 2001). The degree of cognitive impairment was rated using the Clinical Dementia Rating (CDR) (Hughes et al., 1982) following a clinical interview with patient and a relative as described previously (Wolf et al.,

Department of Psychiatry, *EEG Research Laboratory and †Memory Clinic, Interdisciplinary Center for Clinical Research, Leipzig, Germany; ‡Department of Biological Psychology, Friedrich-Schiller University Jena, Jena, Germany.

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Address correspondence and reprint requests to Dr. Martin Grunwald, University of Leipzig, Department of Psychiatry, EEG-Research Lab, Johannisallee 34, 04103 Leipzig, Germany; e-mail: mgrun@medizin.uni-leipzig.de.

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TABLE 1. Characteristics of the Patient Groups

	Controls CDR 0.0 Mean (SD)	QD CDR 0.5 Mean (SD)	MD CDR 1.0 Mean (SD)
No. of subjects	37	40	44
Female/male	23/14	26/14	28/16
Age (y)	79.50 (2.83)	80.09 (3.68)	76.69 (6.09)
MMSE	28.2 (1.3)	25.6 (1.0)	22.4 (2.0)

CDR, Clinical Dementia Rating; SD, standard deviation; MMSE, Mini-Mental State Examination (Folstein 1975); QD, questionable dementia; MD, mild dementia.

2001). A CDR global score was assigned according to published rules. A CDR global score of 0 indicates no dementia, and CDR global scores of 0.5 to 1 indicate questionable and mild dementia. According to the CDR, the samples were divided into three groups: 37 controls (C, CDR = 0), 40 patients with questionable dementia (QD, CDR = 0.5), and 44 patients with mild dementia (MD, CDR = 1). All patients with a CDR global score of 1 were diagnosed with AD according to the research criteria of the ICD-10. This sample included 39 subjects from our preliminary sample (Grunwald et al., 2001). Demographic and neuropsychiatric characteristics of the groups are shown in Table 1. The study was approved by the local ethics committee. All subjects gave written informed consent to participate in this study.

EEG Recording and Parameters

EEG recordings were performed 102 ± 169 days before the MRI study. The EEG data recording procedure was similar to that described in a previous report (Grunwald et al.; 2001). Segmentation of EEG data and subsequent calculations of the mean spectral power density were performed with the EEG analytical software package Brain Vision (Brain Products, Munich, Germany). Artifact-free segments of 1.53 seconds (256 samples/channel) of the rest period were chosen after automatic artifact rejection. For the artifact rejection, an amplitude criterion of ± 70 μV was chosen. 150 to 250 artifact-free EEG-segments per subject under rest conditions were used for spectral analysis. The segments were submitted to a fast Fourier transform analysis. Mean spectral absolute power (μV^2) was calculated as the mean amplitude of the spectral lines of the EEG bands (theta: 4.0–8.0 Hz, alpha: 8.0–13.Hz, beta: 13–24Hz). The mean spectral power parameters per channel and per subject were ln10-transformed before statistical analysis.

Magnetic Resonance Imaging

MRI Acquisition

Within 4 months after the clinical assessment, all participants were investigated by a 1.5 T tomograph (Siemens Vision) with a volumetric T1-weighted-MPRAGE sequence (TR 11.4 milliseconds, TE 4.4 milliseconds, 128 slices, orientation transverse, matrix 256 × 256, voxel size 0.9 × 0.9 × 1.5 mm).

Analysis of MRI Data Sets

Datasets were analyzed using in-house software of the Max-Planck-Institute of Human Cognitive and Brain Sciences in Leipzig, Germany (Mon-A) without knowing the cognitive state or other clinical data of the participants.

The T1-weighted data sets were aligned with the stereotactical coordinate system and interpolated to an isotropical voxel size of 1 mm using fourth-order b-spline interpolation. Six cross sections of the hippocampus were manually outlined in the coronal plane on both sides (by A.H.). Hippocampal measures started behind the amygdala at the slice in which the area of the hippocampal head appeared maximal and were continued posteriorly at 3-mm intervals. The first two measured hippocampal segments are located in the anterior part of the hippocampus. The manual outlining technique of the hippocampus has previously been shown to have a high interrater reliability with an intraclass correlation coefficient of 0.996 (Wolf et al., 2001, 2004). To yield an estimate of the hippocampal volumes (HcV), areas one to six were multiplied by slice thickness (3 mm) and summed on each side (HcVL, resp. HcVR). The HcVR and HcVL per subject were ln10-transformed before statistical analysis.

In a large subsample of subjects (n = 104), the brain volume was determined using a previously described automated region growing segmentation method (Wolf et al., 2003).

Statistical Evaluation

All statistical analyses were conducted using the SPSS for Windows (version 10.0.7). To evaluate correlations between ln10-transformed EEG-data and ln10-transformed hippocampal volumes on each side throughout the entire sample (N = 121), partial correlation coefficients of these parameters were computed and controlled for gender, age (Juarez and Corsi–Cabrera 1995, Coffey et al., 1998), and interval between MRI and EEG.

Eight single correlations per side (left, right) were calculated. Therefore, the critical alpha was adapted to a' = 0.006 (a/8). Because we used directed hypotheses, one-tailed tests were performed for the partial correlation.

To evaluate correlations between ln10-transformed theta power and ln10-tranformed global brain volumes (BV), we used the data set of a subsample of 104 subjects. The partial correlations of 19 single tests were calculated (BV × 19 channel). The critical alpha was adapted to a' = 0.002 (a/19).

RESULTS

Within the entire sample (N = 121), partial correlation analysis (corrected for gender, age, time interval between MRI and EEG) between right hippocampal volume (HcVR) and spectral power of the theta band (right-side electrode positions revealed significant negative correlations [critical a' <0.006] for frontal electrodes Fp2, F4; Fig 1). Partial correlations between left hippocampal volume (HcVL) and spectral power of the theta band (left side electrode positions) were significantly negative (critical a' <0.006) for all left side electrodes (Fig 1). Partial correlation coefficients of all

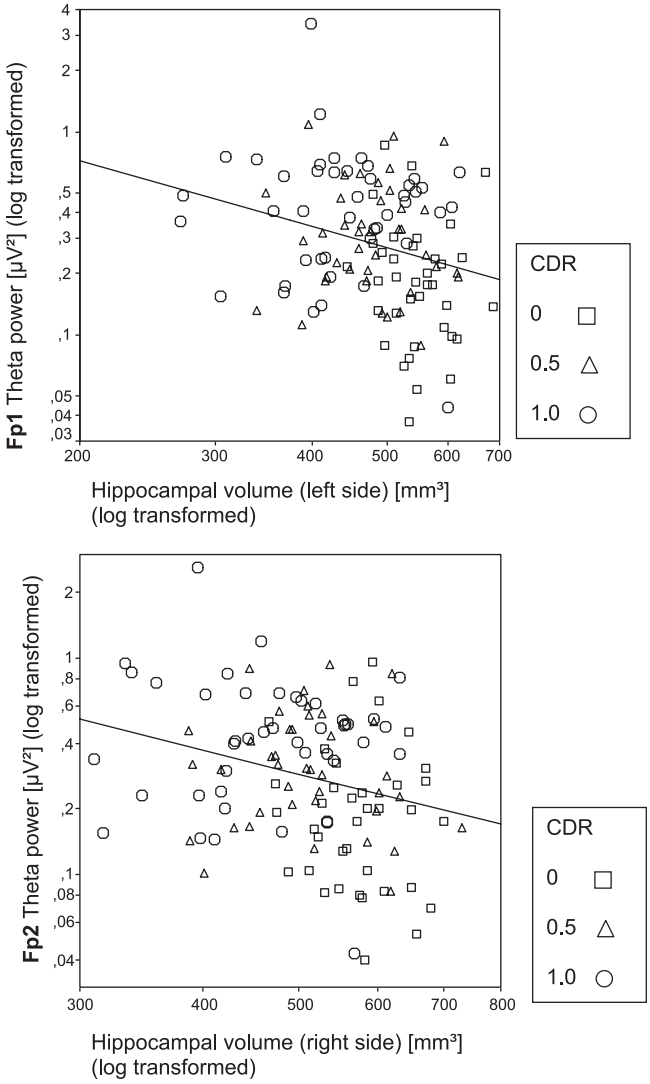

FIGURE 1. Regression plot for significant linear correlations between right hippocampal volumes and right-frontal theta power (Fp2) and between left hippocampal volumes and left-frontal theta power (Fp1).

comparisons are shown in Table 2. For spectral power of the alpha band and beta band, no significant correlation coefficients were found.

No significant correlation was found between the theta power and the global brain volume (BV) in a subsample of n = 104.

DISCUSSION

The main results of the present study are significant negative correlations between the theta power (left/right side) and the hippocampal volume (left/right side). This is in accordance with our previous results (Grunwald et al., 2001) that the increase of theta power at different stages of memory impairment is primarily associated with an atrophy of the hippocampus. Impressively, this study not only replicates the results of the previous study in a much bigger sample (N = 121), but also extends those results by significant negative correlations between size of the hippocampus and theta power for all left side electrodes. Two frontal electrodes on the right side reached the critical alpha level (a' <0.006). However, the r values of the partial correlations are relatively low. The explained variance is on average 7%.

TABLE 2. Partial Correlation Coefficients (Corrected for Age, Gender, and Time Interval Between MRI and EEG) Between Spectral Power of Theta Band (μV^2) and Hippocampal Volume (mm^3)

	Left Side			Right Side	
Channel	**r Value**	***P* Value**	**Channel**	**r Value**	***P* Value**
Fp1	−0.270	0.002	Fp2	−0.270	0.002
F3	−0.260	0.002	F4	−0.236	0.005
F7	−0.276	0.001	F8	−0.135	0.072
C3	−0.263	0.002	C4	−0.188	0.020
P3	−0.265	0.002	P4	−0.184	0.023
T3	−0.272	0.001	T4	−0.150	0.052
T5	−0.257	0.002	T6	−0.159	0.042
O1	−0.282	0.001	O2	−0.192	0.018

P value is the one-tailed significance of partial correlation coefficients.

No significant correlation was found between theta power and the global brain volume in a subsample of 104 subjects. These results confirm the hypothesis that the relationship between cortical theta activity and the hippocampal volume is not is not mediated through the global brain volume.

We conclude for both hemispheres that theta activity is associated with hippocampal volume. A small hippocampal volume is correlated with a higher cortical theta power and *vice versa*. This result is specific for the theta activity because we have not found any significant correlations between hippocampal volume and alpha or beta power. This is in line with previous results (Grunwald et al., 2001).

It is well known that the theta activity in neocortical regions is induced by synchronized bursts of a small set of hippocampal pyramidal cells in the CA1 field, controlled by the medial and lateral septum (Bland et al., 1999; Vinogradova 1995) and regulated by hippocampo-cortical feedback loops (Grunwald et al.; 2002, Klimesch et al. 1996; Lopes da Silva 1992; Miller 1991; Stewart and Fox, 1990). Although neuropathological mechanisms leading to an increase of cortical theta activity in humans at different stages of cognitive impairment are not completely understood, it seems comprehensible that the striking increase of synchronized hippocampal theta activity in these patients might reflect a process of degeneration, particularly of inhibitory interneurons in the CA1 field. Rae–Grant et al. (1987) provided some evidence for a possible connection between cortical theta activity and hippocampal atrophy. In their study, a high correlation between theta activity and an excessive neuronal loss in hippocampi was found at autopsy in AD patients. It might be assumed that the atrophy of the hippocampal formation is mainly due to a loss of neurons primarily in the CA1 region (Fukutani et al., 1995; Jack et al.,

2002; Price et al., 2001; Velez–Pardo et al., 2004; Wang et al., 2003), even in different stages of AD (Brady and Mufson 1991; Bobinski et al., 1995; Jack et al., 2000; Jobst et al., 1992, 1994).

A direct link between loss of CA1 neurons and changes of slow wave brain electrical activity was shown only in epileptic research. Diehl et al. (2002) showed relationships between brain electrical seizure spikes and cell loss in the hippocampal CA1 area in patients with hippocampal sclerosis. These investigators found a significant correlation between the amount of cell loss in CA1 and frontotemporal spikes.

Whether the neuronal loss in the hippocampus is an epiphenomenon for the increase on theta activity or whether it is the causal reason cannot be distinguished on the basis of our data. The epiphenomenologic interpretation is that cortical theta activity can be generated independently of the hippocampus, e.g., in the cingulate cortex (Pizzagalli et al., 2003; Talk et al., 2004). This is in line with Kirk and Mackay's (2003) animal and human study findings that cortical theta activity is generated independently by two different networks, the hippocampo-anterior thalamic system and the perirhinal-mediodorsal thalamic system. Bastiaansen and Hagoort (2003) suggested that the cortical theta activity reflects an interplay between hippocampal and cortical generators whereby the theta generator(s) in the neocortex can produce theta activity by itself independently of or in relation to the hippocampal generators. We cannot exclude that the increased theta activity found for different forms of cognitive impairment in older subjects or in AD patients is caused by changes in other cortical regions and not by atrophy in the hippocampus.

A limitation of our study is the small spatial resolution of the EEG and the individual variation of electrode placements in relation to the brain anatomy. We used only the standard clinical resolution of the 10 to 20 system (19 electrodes). By this means, a strong spatial attribution between EEG signals and brain anatomy cannot to be guaranteed. However, the cortical theta activity is not strongly focalized but rather involves broader cortical networks. Therefore, it seems reasonable to conclude that we were able to detect the related changes in the brain regions.

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