Journal of Clinical Neurophysiology
18(02):178–184, Lippincott Williams & Wilkins, Inc., Philadelphia

Correlation Between Cortical θ Activity and Hippocampal Volumes in Health, Mild Cognitive Impairment, and Mild Dementia

*M. Grunwald, *F. Busse, *A. Hensel, †F. Kruggel, ‡S. Riedel–Heller, ¶H. Wolf, §T. Arendt, and *H.- J. Gertz

*University of Leipzig, Department of Psychiatry, *EEG-Research Laboratory and Memory Clinic, ‡Research Department of Evaluation, Epidemiology; §Paul-Flechsig-Institute of Brain Research; and ¶Department of Neurology; and the †Max-Planck-Institute of Cognitive Neuroscience, Leipzig, Germany.*

Summary: Cognitive decline is known to be associated with both increased θ power over frontal regions and hippocampal atrophy. The aim of this study was to reveal the relation between these parameters in groups with mild dementia, mild cognitive impairment, and healthy control subjects. The authors examined a preliminary randomly selected sample of 39 right-handed subjects joining the Leipzig Longitudinal Study of the Aged, consisting of 17 normal elderly subjects, 12 patients with mild cognitive impairment, and 10 patients with mild dementia assessed by Clinical Dementia Rating. All subjects were between 75 and 85 years old (mean age, 78 years; standard deviation, 2.78 years) and underwent EEG and brain MRI. Mean spectral power densities were calculated, and hippocampal body volume was measured. Significant negative linear correlations between θ power over frontal regions and hippocampal volumes were found. The results support the assumption about a relationship between hippocampal atrophy and θ power, and may be helpful for a better understanding of the course of Alzheimer's disease. **Key Words:** Cortical θ—EEG—Hippocampus—Mild cognitive impairment—Mild dementia.

Several studies described two relevant parameters that discriminate patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy control subjects: increased electrical activity in the θ band in AD and decrease of hippocampal body volume (HVB) (Förstl et al., 1996; Prichep et al., 1994) .

The increase in θ activity is a typical finding in AD and MCI patients. Discriminant analyses proved θ activity as the best discriminating electrophysiologic parameter between AD patients, MCI patients, and healthy control subjects. Theta activity in these groups is highly correlated with loss of memory function (Jelic et al., 1996, 1998). Generally, there is a direct relation between memory function and θ activity (Grunwald et al., 1999; Mecklinger et al., 1992).

Hippocampal atrophy is a common finding in computed tomography and MRI studies of patients with AD and MCI (Bobinski et al., 1995; de Leon et al., 1993; Jack et al., 1997; Kesslak et al., 1991; Killiany et al., 1993; Strijers et al., 1997). In MRI studies, a marked decrease in hippocampal volume was found. De Leon et al. (1997) described a loss of hippocampal volume of 14% for the MCI group and 22% for the AD group compared with normal control subjects. Hippocampal atrophy is also observed in normal aging, and in aging associated with mild memory impairment (Golomb et al.,

Supported by funds of the Interdisciplinary Center for Clinical Research at the University of Leipzig (project no. C8).

Address correspondence to Dr. Martin Grunwald, University of Leipzig, Department of Psychiatry, EEG-Research Laboratory,Memory Clinic, Emilienstraβe 14, 04107 Leipzig, Germany.

1993, 1994). Several studies suggest that the atrophy of the hippocampal formation progresses linearly, even during the final stage of AD (Bobinski et al., 1995; Brady and Mufson, 1991; Jobst et al., 1992, 1994).

Functional relations seem to exist between cortical θ activity and the hippocampus. Direct connections seem to exist between the neocortex and the hippocampus. Miller (1991) suggests that direct posterior pathways exist behind the corpus callosum that transmit oscillations from the hippocampus to the neocortical regions. The slow-wave rhythmic activity in the θ band (4–7 Hz) of the hippocampus is localized in the CA1 field of the hippocampus (Duvernoy, 1988), and is controlled by the medial and lateral septum (Bland et al., 1999; Vinogradova, 1995). Two studies provide evidence for a connection between θ activity and hippocampal atrophy. A high correlation between θ 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 neuronal loss in the CA1 field may lead to changes in the slow-wave activity of the neocortex.

However, no reports have been provided so far concerning the relationship between a decreased HBV measured by MRI and EEG spectral θ power in groups with different degrees of cognitive impairment. We assume that a decrease of HBV correlates with an increase of cortical θ activity over frontal regions. We therefore evaluated the relation between θ activity and hippocampal atrophy in groups with MCI, mild dementia (MD), and healthy control subjects.

METHODS

Subjects

A preliminary, randomly selected sample of 39 right-handed subjects joining the Leipzig Longitudinal Study of the Aged (Riedel–Heller et al., 1999) was examined. All subjects were between 75 and 85 years old (mean age, 78 years; standard deviation, 2.78 years), and had Mini-Mental State Examination scores more than 18 points. Exclusion criteria were physical and/or neurologic disabilities (such as blindness, deafness, severe movement disorders, or paralysis) that would have interfered with the ability of the subject to complete neuropsychological tests or paraclinical examinations (such as computed tomographic, EEG or MRI procedures). All subjects were examined medically and neurologically by a trained physician and/or neurologist/psychiatrist. During the neurologic examination, focal neurologic signs and symptoms, gait, balance, primitive reflexes, and extrapyramidal signs were assessed. Psychiatric assessment included the completion of the Montgomery–Asberg Depression Scale (Montgomery and Asberg, 1979) and a semistructured interview to assess cognitive and functional abilities of the subject. A semistructured, detailed medical history was obtained, and the following rating scales were completed: a brief screen for psychosis and major depression based on the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised, criteria (American Psychiatric Association, 1987), the Clinical Dementia Rating (CDR) (Berg, 1984), and the Mini-Mental State Examination (Folstein et al., 1975). The CDR is a 5-point scale with the following scores: 0, normal cognition; 0.5, questionable dementia, mild cognitive impairment; 1, mild dementia; 2, dementia; and 3, severe dementia. Using the staging procedure of CDR, all subjects were classified: The sample consisted of normal elderly control subjects (CDR, 0 point; n = 17), MCI patients (CDR, 0.5 point; n = 12), and MD patients (CDR, 1 point; n = 10). Patients with a CDR of 2 or 3 points were excluded. All patients with a CDR of 1 point were diagnosed as having AD according to the criteria of the NINCDS-ADRDA Work Group (McKhann et al., 1984). Demographic and neuropsychiatric characteristics of the groups are shown in Table 1.

TABLE 1. *Characteristics of the groups, hippocampal volumes, and results of ANOVA*

Variable	Control subjects, CDR 0.0, mean (SD)	MCI patients, CDR 0.5, mean (SD)	MD patients, CDR 1.0, mean (SD)
n	17	12	10
Female/male	13/4	10/2	6/4
Age, y	78.4 (3.1)	78.5 (2.2)	78.2 (2.9)
MMSE, pt.*†‡	28.2 (1.3)	25.6 (1.0)	22.4 (2.0)
Left, mm^{2}*†‡	413.97 (53.39)	354.74 (42.39)	297.59 (46.63)
Right, mm^{2}‡	427.42 (66.28)	379.30 (41.31)	316.89 (62.64)

Analysis of variance post hoc significance: * Controls > MCI; † MCI > MD; ‡ Controls > MD; $P < 0.01$.

CDR, Clinical Dementia Rating; SD, standard deviation; MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; MD, mild dementia.

EEG Recording and Parameters

EEG recordings were performed 51 ± 75 days before the MRI study. EEG data were collected in a dimly lit, temperature-controlled, electrically shielded room on a 19-channel EEG polygraph (Walter Graphtek, Halle, Germany) with the subject in a supine position during a 10-minute resting condition with eyes closed. Data were recorded from 19 Ag–AgC1 saucer-type electrodes placed according to the International 10-20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, T6, P3, Pz, P4, O1, and O2; reference, linked earlobes; sampling rate, 166.6 Hz; time constant, 0.3 seconds; low-pass filter, 70 Hz). Horizontal and vertical eye movements were recorded from bipolar montages with the same sampling parameters. Segmentation of EEG data and subsequent calculations of the mean spectral power density was performed with an EEG analytic software package (Rost et al., 1992). Artifact-free segments of 1.53 seconds (256 samples per channel) from the rest period were chosen by visual inspection and were substantiated by cross-correlation analysis between relevant frontal EEG and electro-oculographic electrodes ($r_{crit.} < 0.5$). Fifty to 60 artifact-free EEG segments per subject were used for spectral analysis. The remaining segments were submitted to a fast Fourier transform analysis and smoothed with a 7-point low-pass filter (weights, 1/64, 3/32, 15/64, 5/16, 15/64, 3/32, and 1/64). Mean spectral power densities (in microvolts) were calculated as the mean amplitude of the spectral lines of each EEG band (θ, 4–8 Hz; α, 8–13 Hz; α-1, 8–10 Hz; α-2, 10–13 Hz). The spectral power density parameters were "z-transformed" before statistical analysis (mean, 0; standard deviation, 1). Spectral power densities in the θ band (mean and standard deviation) of the different groups are presented in Table 2.

Neuroanatomic Imaging and Analysis

For each subject, a three-dimensional T1-weighted high-resolution MRI brain dataset was obtained on a Siemens Vision 1.5-T scanner (Siemens, Erlangen, Germany) using a three-dimensional T1-weighted sequence (magnetization prepared rapid gradient echo [MPRAGE]; repetition time, 11.4 msec; echo time, 4.4 msec; 128 slices; matrix, 256 × 256; voxel size, 0.9 × 0.9 × 1.5 mm). Collected datasets were analyzed with the BRAIN system (Kruggel and Lohmann, 1996). Datasets were aligned with the stereotactic coordinate system by identifying the cross-point of the anterior and posterior commissure in the midsagittal plane and the angular misrotation along the body and the sagittal axes (Talairach and Tournoux, 1988). Using these parameters, an affine transformation was defined to rotate, translate, and interpolate the brain dataset to an isotropic voxel resolution of 1 mm. The intracranial compartments, gray matter, white matter, internal and external cisterns (cerebrospinal fluid compartments) were determined auto-

TABLE 2. *Spectral power density in the θ band*

	Control subjects		MCI		MD			
Channel, μV	Mean	SD	Mean	SD	Mean	SD	F value	*P* Value
Fp1*	3.24	1.48	3.52	1.27	4.85	2.00	3.202	0.052
O2	4.18	1.93	3.90	1.70	6.18	4.02	1.546	0.227
F7	3.27	1.53	3.34	1.29	5.01	3.02	1.755	0.187
F8	3.07	1.90	2.69	1.06	4.34	2.35	2.277	0.117
T3	3.13	2.06	2.83	1.02	4.89	3.24	1.688	0.199
T4	2.84	2.05	2.26	1.01	3.91	2.33	2.044	0.144
T5	3.98	1.89	3.45	1.42	5.96	3.66	2.132	0.133
T6	3.74	2.11	3.59	1.95	5.45	3.22	1.588	0.218
Fz	3.95	2.15	4.07	1.44	5.57	2.61	1.927	0.160
Cz	4.52	2.51	4.36	1.49	6.14	3.01	1.517	0.233
Pz	4.33	2.23	3.95	1.41	6.25	3.53	1.951	0.157
Fp2*	3.19	1.62	3.47	1.19	4.83	1.91	3.748	0.033
F3	3.81	2.08	3.91	1.28	5.43	2.54	2.103	0.137
F4	3.71	2.04	3.76	1.31	5.31	2.58	2.079	0.140
C3	4.07	2.28	3.96	1.23	5.81	3.00	1.846	0.172
C4	4.04	2.33	3.66	1.36	5.58	2.96	1.713	0.195
P3	4.17	1.99	3.65	1.12	6.51	3.86	2.593	0.089
P4	4.30	2.24	3.4	1.68	6.30	3.62	1.912	0.162
O1	4.27	2.00	3.64	1.19	6.39	3.95	2.299	0.115

Analysis of variance post hoc significance: * Controls < MD, $P < 0.05$.
SD, standard deviation; MCI, mild cognitive impairment; MD, mild dementia.

matically using a boundary-guided region-growing procedure (Hojjatoleslami et al., 1999). The intracranial volume was defined as the sum of the brain volume (BV*) and the cerebral spinal fluid volume (Blüml, et al., 1992). The corrected BV was defined as [(BV*/intracranial volume) × 100]. Cross-sections of the hippocampus were segmented manually in the coronal plane on both sides, starting at the head–body transition of the hippocampus, and progressing posteriorly in five sections at a distance of 3 mm. Areas were summed on each side (hippocampal body volume left [HBVL]*, respectively hippocampal body volume right [HBVR]*) and normalized by the intracranial volume to yield an estimate of the volume of the hippocampal body (HBVL, respectively HBVR).

Statistical Evaluation

All statistical analyses were conducted using the SPSS (Chicago, IL, U.S.A.) package for Windows (version 7.5.2). Tests for significance between groups were performed using an analysis of variance (ANOVA) model followed by Gabriel post hoc analyses to detect differences of means between groups. Z-transformed power data and z-transformed normalized HBV data were used for the ANOVA. The criteria of the homogeneity of variance was fulfilled. The critical α values (Bonferroni) for the ANOVA of the θ power data were a' = 0.002, and for the comparison of the hippocampal body parameters (left and right side) was a' = 0.025. The criteria of the homogeneity of variance was fulfilled.

To evaluate the correlation between EEG data and HBV on each side (left/right), the partial correlation coefficients were computed and controlled for gender and interval between MRI and EEG. The dependence of BV changes and brain electrical activity on gender has been described in different studies (Coffey et al., 1998; Juarez and Corsi–Cabrera, 1995). For correlation analysis, we used spectral power densities (logarithmic transformed [ln10(x)]) and normalized HBV parameters (ln10[HBVL] or ln10[HBVL]). According to our hypothesis, the correlation HBVL/Fp1, F7, F3 and HBVR/Fp2, F8, F4 was assessed. Because of the number of the single tests, the critical α value was a' = 0.008 (Bonferroni corrected).

RESULTS

No significant group effects were found for age ($F[2,36] = 0.037$; $P = 0.964$). Significant group effects were found for Mini-Mental State Examination score ($F[2,36] = 50.47$, $P = 0.000$).

The HBVL and the HBVR for control subjects, MCI patients, and MD patients are shown in Table 1. ANOVA revealed significant differences between the groups in the volumes of both hippocampal bodies (right side: $F[2,38] = 18.52$, $P = 0.000$; left side: $F[2,38] = 11.19$, $P = 0.000$). These results are consistent with the results of Helkala et al. (1996). The posthoc results of ANOVA are shown in Table 1. Patients with MD had a significantly smaller HBVL than control subjects and patients with MCI. Patients with MCI had a significantly smaller HBVL than control subjects (left: control subjects > MCI > MD). Patients with MD had a smaller HBVR than the control group. No significant differences in HBVR were observed between control subjects and MCI patients as well as between MCI patients and MD patients (right: control subjects > MD; see Table 1).

ANOVA results showed no significant group effects for the spectral θ power. No test reached the critical α level. Results of ANOVA are shown in Table 2.

Partial correlation coefficients (corrected for gender and interval between EEG measurement and MR image) between HBVL and spectral power density of the θ band (left frontal electrode positions: Fp1, F7, F3) were significant for electrode Fp1. HBVR and spectral power density of the θ band (right frontal electrode positions: Fp2, F8, F4) showed a significant correlation for Fp2, F8, and F4.

Moreover, significant correlations were found between HBVR and θ power for the electrodes C4, Fz, and Cz ($P < 0.05$). All these correlations were negative. The correlation coefficient for the HBVR and the right frontal θ power (Fp2) was significant ($P = 0.005$; $r = -0.4134$). Therefore, the critical α (a' = 0.008) fell short of one correlation test. This means that the hypothesis of a linear relation between the variables can be affirmed. Partial correlation coefficients of all comparisons are compiled in Table 3. Four significant linear correlations are shown by example in Fig. 1.

For spectral power density of the α band, the α-1 band, and the α-2 band, no significant correlation coefficients were found.

DISCUSSION

A negative correlation was found between the HBV and the spectral power density in the θ band in the corresponding frontal regions. A negative correlation existed in seven comparisons. The HBVR was correlated with θ activity over the right frontal lobe (Fp2, F4, F8), over the right central regions (C4), and over the midfrontal regions (Fz, Cz). On the left side, the HBV correlated significantly with the θ activity over the left

TABLE 3. *Partial correlation coefficients (corrected for gender and time interval between MRI and EEG) between spectral power density of θ band and hippocampal body volume*

Hippocampal body volume, mm^2					
Left side			Right side		
θ channel	*r* value	*P* value	θ channel	*r* value	*P* value
Fp1	−0.2778	0.048	Fp2	−0.4134	0.005
F3	−0.2268	0.089	F4	−0.3193	0.027
F7	−0.2406	0.076	F8	−0.2806	0.046
P3	−0.2567	0.063	C4	−0.2960	0.038
C3	−0.2400	0.076	P4	−0.2704	0.053
T3	−0.2330	0.083	T4	−0.2495	0.058
T5	−0.2112	0.105	T6	−0.2441	0.073
O1	−0.2433	0.073	O2	−0.2196	0.096
Fz	−0.2479	0.070		−0.3327	.022
Cz	−0.2317	0.084		−0.3062	0.033
Pz	−0.2394	0.077		−0.2734	0.051

P = one-tailed significance of partial correlation coefficients.

frontal lobe (Fp1). Our observations were specific for the θ band because no correlations were revealed for the α, α-1, and α-2 bands. We conclude that in our groups hippocampal atrophy corresponded with increased frontal cortical θ activity in both hemispheres in dementia and other degrees of cognitive impairment. Neuropathologic mechanisms leading to an increase of cortical θ activity in humans are not completely understood so far. However, it is known that the slowing of the dominant EEG rhythm in dementia patients correlates with a general reduction in cortical metabolic activity (Buchan et al., 1997; Dierks et al., 1991, Elmstahl et al., 1994). This relationship is described particularly for the left-brain regions. The decrease in the volume of the hippocampal subdivisions correlated with the neuronal loss and the percentage of neurons without neurofibrillary changes, but not with the numeric density or total number of

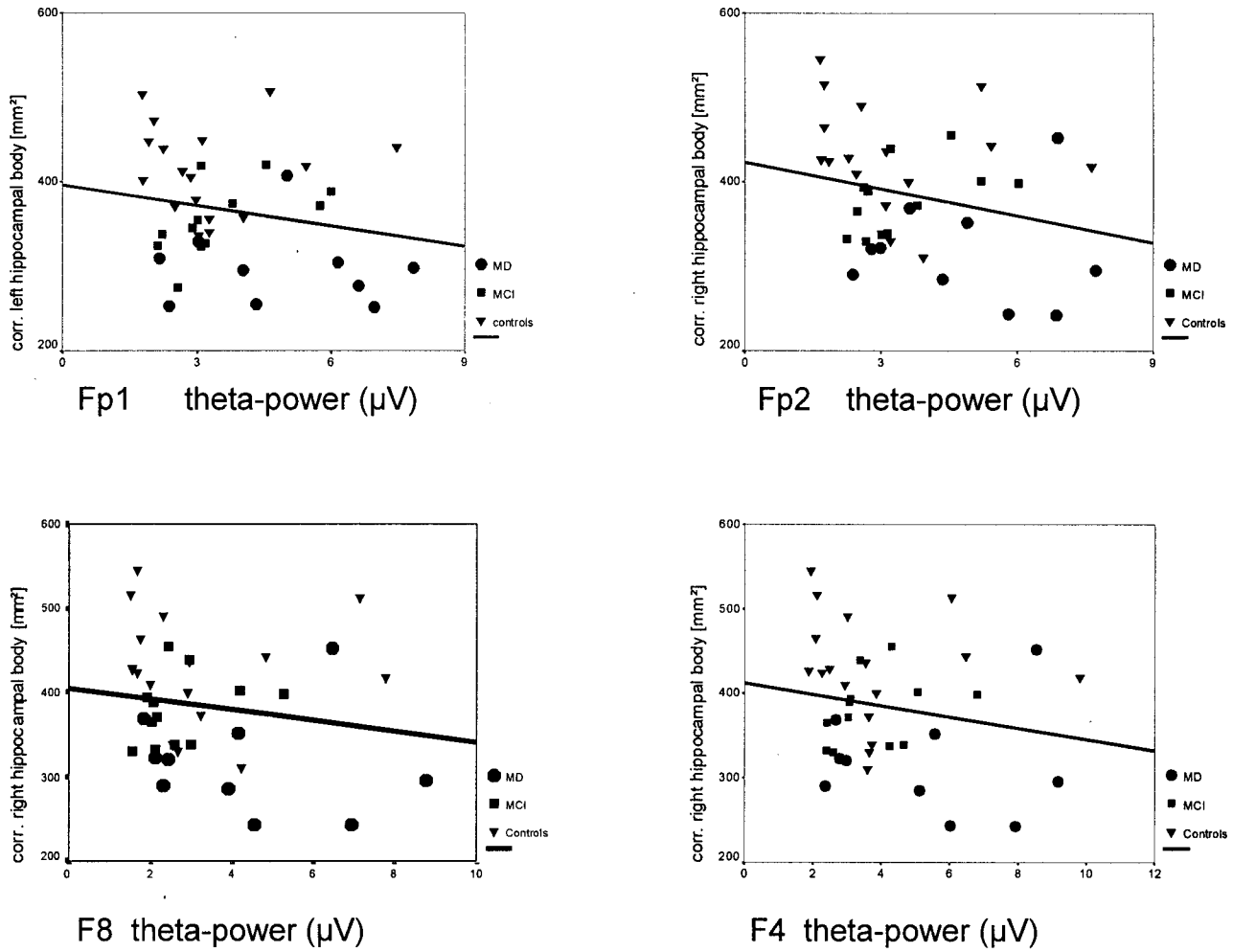

FIG. 1. Regression plot for significant linear correlations between right hippocampal volumes and right-frontal θ power (Fp2, F4, F8), and between left hippocampal volumes and left-frontal θ power (Fp1).

plaques or the amyloid burden (de Leon et al., 1997). Therefore, the linear relationship between θ activity and HBV in our data may be the result of neuronal loss in hippocampus, particularly of neurons in the CA1 field (Bobinski et al., 1995). Possibly, the striking increase of synchronized hippocampal θ activity reflects the process of degeneration, particularly of inhibitory interneurones in the CA1 field. Therefore, septal input cannot be processed adequately (Bösel, 1993; Creutzfeldt, 1993; Duvernoy, 1988). The θ activity in neocortical regions is induced by synchronized bursts of a small set of hippocampal pyramidal cells in the CA1 field and is regulated by hippocampocortical feedback loops (Klimesch et al., 1996; Lopes da Silva, 1992; Miller, 1991; Stewart and Fox, 1990). On the basis of the current knowledge, this argument has to be seen as hypothetical.

Descriptive statistics of intergroup comparisons revealed for both HBV and θ activity different results: Regarding HBVL, it turns out that there were significant differences between all groups (see Table 1) as shown by others (de Leon et al., 1997). The MD group differed in spectral θ power density from the control group over the left and the right frontal regions (Fp1, Fp2). These tests did not reach the critical α level. These data agree with previous reports about an increase of slow EEG activity over frontal regions during the progression of dementia (Besthorn et al., 1994; Wada et al., 1998).

The linear trend between hippocampal atrophy and θ activity in the current study supports the assumption that both processes may be linked. Both parameters may be helpful for a better understanding of the course of AD. However, mechanisms leading to increased θ activity in hippocampal atrophy remain unclear and require further investigation.

Acknowledgment: For technical support the authors gratefully thank I. Thomas (EEG research laboratory) and the Department of Radiology at the University of Leipzig.

REFERENCES

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 3rd ed., rev. Washington, DC: American Psychiatric Press, 1987.*

Berg L. Clinical Dementia Rating [letter]. Br J Psychiatry 1984;145: 339.

Besthorn C, Forstl H, Geiger–Kabisch C, et al. EEG coherence in Alzheimer disease. *Electroencephalogr Clin Neurophysiol* 1994; 90:242–5.

Bland BH, Oddie SD, Colom LV. Mechanisms of neural synchrony in the septohippocampal pathways underlying hippocampal theta generation. *J Neurosci* 1999;19:3223–37.

Blüml S, Schad LR, Betsch B, et al. Segmentation and determination of brain compartment volumes using 3D gradient echo sequences. 4263. *SMRM. Society of Magnetic Resonance Imaging in Medicine: works in progress.* Berlin: Springer, 1992.

Bobinski M, Wegiel J, Wisniewski HM, et al. Atrophy of hippocampal formation subdivisions correlates with stage and duration of Alzheimer disease. *Dementia* 1995;6:205–10.

Bösel R. Die cerebrale Theta–Rhytmizität unterstützt kontextabhängige Diskriminationsleistungen. *Kognitionswissenschaft* 1993;3:83–94.

Brady DR, Mufson EJ. Alz-50 immunoreactive neuropil differentiates hippocampal complex subfields in Alzheimer's disease. *J Comp Neurol* 1991;305:489–507.

Buchan RJ, Nagata K, Yokoyama E, et al. Regional correlations between the EEG and oxygen metabolism in dementia of Alzheimer's type. *Electroencephalogr Clin Neurophysiol* 1997;103: 409–17.

Coffey CE, Lucke JF, Saxton JA, et al. Sex differences in brain aging: a quantitative magnetic resonance imaging study. *Arch Neurol* 1998;55:169–79.

Creutzfeldt O. Cortex cerebri: performance, structural an functional organization of the cortex. Göttingen: Hubert & Co., 1993.

de Leon MJ, George AE, Golomb J, et al. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiol Aging* 1997;18:1–11.

de Leon MJ, Golomb J, George AE, et al. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. *AJNR Am J Neuroradiol* 1993;14:897–906.

Dierks T, Perisic I, Fröhlich L, et al. Topography of the quantitative electroencephalogram in dementia of the Alzheimer type: relation to severity of dementia. *Psychiatry Res* 1991;40:181–94.

Duvernoy HM. *The human hippocampus: an atlas of applied anatomy.* München: JF Bergmann, 1988.

Elmstahl S, Rosen I, Gullberg B. Quantitative EEG in elderly patients with Alzheimer's disease and healthy control subjects. *Dementia* 1994;5:119–24.

Folstein MF, Folstein SE, McHugh PR. "Min-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatry Res* 1975;12:189–98.

Förstl H, Besthorn C, Sattel H, et al. Volumetric brain changes and quantitative EEG in normal aging and Alzheimer's dementia. *Nervenarzt* 1996;67:53–61.

Golomb J, de Leon MJ, George AE, et al. Hippocampal atrophy correlates with severe cognitive impairment in elderly patients with suspected normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry* 1994;57:590–3.

Golomb J, de Leon MJ, Kluger A, et al. Hippocampal atrophy in normal aging. An association with recent memory impairment. *Arch Neurol* 1993;50:967–73.

Grunwald M, Weiss T, Krause W, et al. Power of theta waves in the EEG of human subjects increases during recall of haptic information. *Neurosci Lett* 1999;260:189–92.

Helkala EL, Hanninen T, Hallikainen M, et al. Slow-wave activity in the spectral analysis of the electroencephalogram and volumes of hippocampus in subgroups of Alzheimer's disease patients. *Behav Neurosci* 1996;110:1235–43.

Hojjatoleslami SA, Kruggel F, von Cramon DY. Segmentation of white matter lesions from volumetric MR images. In: Talyor C, Colchester A, eds. *Medical image computing and computer-aided intervention*. Vol. 1679. Heidelberg: Springer 1999:52–61.

Jack CR Jr, Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997;49:786–94.

Jelic V, Dierks T, Amberla K, et al. Longitudinal changes in quantitative EEG during long-term tacrine treatment of patients with Alzheimer's disease. *Neurosci Lett* 1998;254:85–8.

Jelic V, Shigeta M, Julin P, et al. Quantitative electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment. *Dementia* 1996;7:314–23.

Jobst KA, Smith AD, Szatmari M, et al. Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. *Lancet* 1992;340: 1179–83.

Jobst KA, Smith AD, Szatmari M, et al. Rapidly progressing atrophy of

medial temporal lobe in Alzheimer's disease. *Lancet* 1994;343: 829–30.
Juarez J, Corsi–Cabrera M. Sex differences in interhemispheric correlation and spectral power of EEG activity. *Brain Res Bull* 1995; 38:149–51.
Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. *Neurology* 1991;41:51–4.
Killiany RJ, Moss MB, Albert MS, et al. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. *Arch Neurol* 1993;50:949–54.
Klimesch W, Doppelmayr M, Russegger H, et al. Theta band power in the human scalp EEG and the encoding of new information. *Neuroreport* 1996;7:1235–40.
Kruggel F, Lohmann G. BRAIN—a toolkit for the analysis of multimodal brain datasets. In: Lemke HU, Inamura K, Jaffe CC, Vannier MW, eds. *Computer assisted radiology*. Paris: Springer, 1996:323–8.
Lopes da Silva FH. The rhythmic slow activity (theta) of the limbic cortex: an oscillation in search of a function. In: Basar E, Bullock TH, eds. *Induced rhythms in the brain*. Boston: Birkhäuser, 1992:83–102.
McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34: 939–44.
Meclinger A, Kramer AF, Strayer DL. Event related potentials and EEG components in a semantic memory search task. *Psychophysiology* 1992;29:104–19.
Miller R. *Cortico-hippocampal interplay and the representation of contexts in the brain*. Berlin: Springer, 1991.
Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
Prichep LS, John ER, Ferris SH, et al. Quantitative EEG correlates of cognitive deterioration in the elderly. *Neurobiol Aging* 1994;15: 85–90.
Rae–Grant A, Blume W, Lau C, et al. The electroencephalogram in Alzheimer-type dementia. A sequential study correlating the electroencephalogram with psychometric and quantitative pathologic data. *Arch Neurol* 1987;44:50–4.
Riedel–Heller SG, Matschinger H, Schork A, et al. Do memory complaints indicate the presence of cognitive impairment? Results of a field study. *Eur Arch Psychiatry Clin Neurosci* 1999;249: 197–204.
Rost R, Hansen E, Beyer L, et al. EEG topography software for description of central nervous activation. In: Haschke W, Speckmann WEJ, Roitbak AI, eds. *Slow brain potentials and magnetic fields*. Jena: Friedrich Schiller University Press, 1992:137–45.
Stewart M, Fox SE. Do septal neurons pace the hippocampal theta rhythm? *Trends Neurosci* 1990;13:163–8.
Strijers RL, Scheltens P, Jonkman EJ, et al. Diagnosing Alzheimer's disease in community-dwelling elderly: a comparison of EEG and MRI. *Dement Geriatr Cogn Disord* 1997;8:198–202.
Talairach J, Tournoux P. *Co-planar stereotactic atlas of the human brain*. New York: Thieme, 1988.
Vinogradova OS. Expression, control, and probable functional significance of the neuronal theta-rhythm. *Prog Neurobiol* 1995;45: 523–83.
Wada Y, Nanbu Y, Kikuchi M, et al. Abnormal functional connectivity in Alzheimer's disease: intrahemispheric EEG coherence during rest and photic stimulation. *Eur Arch Psychiatry Clin Neurosci* 1998;248:203–8.