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A comparison of qEEG and HMPAO-SPECT in relation to the clinical severity of Alzheimer's disease

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Abstract Electroencephalographical studies have disclosed correlations between topographical features of Fast Fourier Transformation maps and the severity of Alzheimer's disease (DAT). The object of the present study was to explore the relations of HMPAO-SPECT and quantitative EEG (qEEG) with the severity of dementia. Twenty-three patients were included in the study. Spectral and topographical EEG parameters were compared with global and regional cerebral blood flow, and with psychometric measures of clinical serverity. None of the regions of interest of the SPECT scans were significantly correlated with clinical severity. Low values in delta- and theta-bands, however, were related to high scores on the Mini-Mental-State examination ($P < 0.01$), whereas the Syndrom-Kurz test correlated inversely with the power values in the alpha and beta band. The global decrease in cerebral blood flow (CBF) was associated with a shift on the topographical alpha-centroids in the posterior direction ($P < 0.01$). In previous studies correlations between CBF and clinical severity were weak, indicating a high interindividual variance, or interactions with concomitant vascular lesions. Whereas SPECT is a well-established tool for the diagnosis of dementia, the present study indicates qEEG as a potential marker for the staging of the cognitive decline in DAT.

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Introduction

Alzheimer's disease (DAT) causes a typical pattern of macroscopic changes in the brain. Anatomical studies disclose atrophy of cortical structures, initially of the temporal lobes, and, as the disease progresses, of the frontal and parietal lobes. Basal structures are affected only in late stages, whereas occipital areas and the cerebellum are almost spared of macroscopic deterioration (Mann et al. 1994). The degree of these changes can be assessed in vivo with structural and functional brain imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT). In particular, SPECT has been considered to be the gold standard for the diagnosis of DAT since it allows investigation of regional cerebral blood flow (rCBF) and determination of the degree of brain damage (Waldemar et al. 1994). However, the link of the findings with stage and course of disease has not yet been sufficiently clarified (Maurer et al. 1991). For example, the correlations of rCBF with the cognitive performance in neuropsychological tests were not consistent (Waldemar et al. 1994; Montaldi et al. 1990; O'Brien et al. 1992).

EEG brain mapping is a sensible tool to measure functional changes of brain activity in real time. This method has allowed description and quantification of some typical features in DAT, such as an increase in theta and delta activity in frontal electrode sites first, extending to parietal electrode positions in later stages of the disease. Alpha and beta activity has been shown to generally decrease along with an increasing shift towards anterior regions of the centre of gravity of the alpha-band. Maurer and Dierks (1991) and Dierks et al. (1991) demonstrated that differences in the topographical pattern of the alpha and beta band were related to the severity of dementia, and hypothesised a possible predictive value of these features. These findings were substantially confirmed by a recent study (Chiaramonti et al. 1997). Independent from frequency analysis, in the time domain and with a resolution in the millisecond range, consistent anteriorisations of the brain electrical fields which correlated with clinical severity were found with the adaptive spatial segmentation of the EEG (Strik et al. 1997). Martin-Loeches et al. (1991) showed that brain activity slowings were focalised in multiinfarct dementia (MID), whereas patients with DAT showed a more generalised pattern. In most studies it has been possible to distinguish elderly patients from patients with severe dementia. However, until now it has not been possible to distinguish the EEG in early stages of dementia from the EEG of elderly persons (Soininen et al. 1991a,b).

The study of the interrelations between complementary methods of investigation is supposed to improve the understanding of the respective findings and to enhance their value in clinical application, e.g. in early diagnosis and staging. Previous studies have revealed significant correlations between theta and delta power and reduced CBF (Stigsby et al. 1981; Kwa et al. 1993; Passero et al. 1995); Soininen et al. (1991a), however, found inconsistent results in subgroups of DAT.

The present study was conducted to investigate the relations of the spontaneous EEG and of SPECT with the clinical severity of DAT as well as the correlations between the methods. In particular, topographical aspects of the qEEG, which have not been correlated with SPECT to date, are the focus. The hypothesis was that there would be a linear and direct correlation between the characteristic results of SPECT and qEEG in DAT.

Methods

Subjects

We examined 23 inpatients of the Department of Psychiatry, University Hospital of Würzburg (Germany). The mean age was 67.2 ± 8.0 years (range 55–81 years), with 18 females and 5 males. They complied with the criteria of mild or moderate probable DAT of the NINCDS/ADRDA inventory (McKhann et al. 1984). This scale scores clinical features with weighted subitems. To exclude patients with MID, the Hachinski scale (Hachinski et al. 1975) was applied. Scores of less than 4 were accepted for inclusion in the study. Relevant concomitant psychiatric and somatic disorders were excluded by history, physical, neurological and psychiatric examination. In particular, patients with a Hamilton depression score exceeding 10 were excluded (Hamilton 1960). Routine blood and serum parameters including thyroid hormone levels were within the normal range. Cranial CT scans were done in every patient. At the time of examination, patients were off psychotropic medication for at least 2 weeks.

Clinical assessment

The German versions of the Mini-Mental State examination (MMSE; Folstein et al. 1975) and of the Syndrom-Kurz test (SKT; Erzigkeit 1989) were applied.

SPECT

In 18 of the 23 cases SPECT with ^{99m}Tc-hexamethylpropyleneamineoxime was performed (HMPAO-SPECT) at the Department of Nuclear Medicine of the University Hospital of Würzburg. Between 30 and 45 min after intravenous injection of 600–800 Mbq Tc-99m-HMPAO SPECT scans were acquired using a single-headed gamma camera (Diacam, Siemens, Erlangen, Germany) in a 360° full circle (64 views, 30 s per view, acquisition matrix of 64 × 64 pixels). For reconstruction of the tomographic images the filtered back projection method was used with a Butterworth filter (cutoff 0.8, order 7). Scan level was set to the nuclei basales. The relative CBF of each region of interest (ROI) was calculated based on the cerebellum as reference area. The ROIs were the fronto-medial, fronto-lateral, temporo-anterior, temporo-posterior, parieto-anterior, parieto-posterior and occipital part of each of the hemispheres. Furthermore, rCBF of the nuclei basales and the limbic system were assessed.

EEG examination

The examination was performed in a low-noise, electrically shielded room. Subjects laid on a bed with their eyes closed. Nineteen Silver–silverchloride electrodes were placed according to the international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) with reference to linked mastoids connected with 10-kOhm resistors each. Impedances were below 2 kOhm. Five minutes of spontaneous EEG was recorded by a BioLogic Brain Atlas System with a digitization rate of 128 Hz and the bandpass set to 1–30 Hz. Ten two-second lasting artefact-free epochs were selected for each subject. To perform the fast Fourier transformation, the algorithm by Press et al. (1993) was implemented in a C-program. The square roots of the power values were averaged for the standard EEG frequency bands (delta: 0–2.5 Hz; theta: 3–7.5 Hz; alpha 8–12.5 Hz; beta: >12.5 Hz). In order to reduce alpha-inflation, only absolute power values were calculated, although in previous studies also correlations with relative power have been described (Leuchter et al. 1993). For each frequency band, the topographical centroids were calculated and the location was quantified based on the coordinates of a planar projection of the electrode grid (see e.g. Lehmann 1987; Strik and Lehmann 1993).

Statistics

Statistics were computed with the Statistica software package. After testing the data for normal distribution, Pearson product-moment correlations were applied; all reported *p*-levels are two-tailed.

Results

The mean score of MMSE was 20.4 ± 6.8 (range 12–25), and of the SKT 15.8 ± 7.2. The rCBF levels of the respective ROIs are displayed in Fig. 1.

Psychometrics and HMPAO-SPECT

No correlations were found between the global and hemispheric CBF and neuropsychological test results.

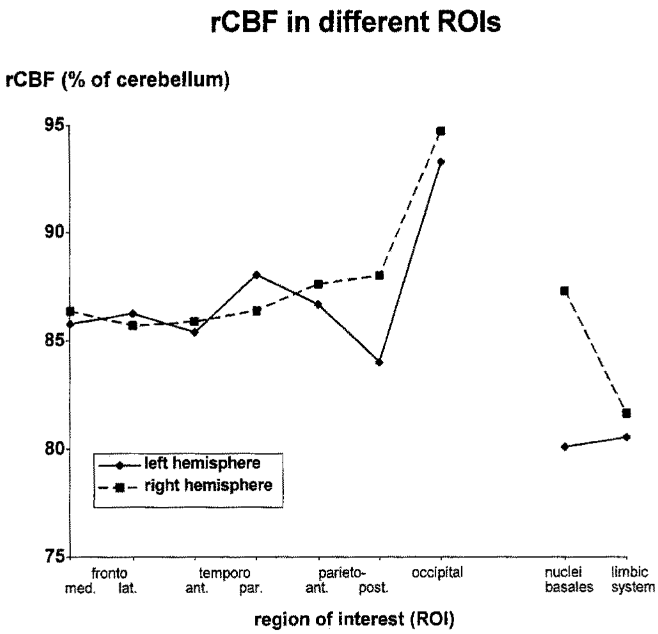

Fig. 1 Regional cerebral blood flow *(rCBF)* of the brain, percentage of reference (cerebellum); *dotted line* right hemisphere; *solid line* left hemisphere; neocortical structures are separated from nuclei basales and limbic system

Psychometrics and EEG

Lower MMSE scores were correlated significantly with higher theta- (r = 0.50, P < 0.05) and delta- (r = 0.64, P < 0.001) power. No correlations were found between MMSE scores and power in the alpha- (r = 0.19, n.s.) and beta- (r = 0.31, n.s.) band. Worse performance in the SKT, on the other hand, was significantly associated with lower alpha- (r = 0.52, P < 0.01) and beta- (r = 0.63, P < 0.01) power. No correlations of this test with slow frequencies were found, however (delta: r = 0.29, n.s.; theta: r = 0.25, n.s.). After Bonferroni correction, all significant correlations remained at a probability below 0.05 with the exception of theta vs MMSE score and alpha-power vs SKT score, which were then at a probability level of 0.06.

The topographical features of the power maps were correlated with the SKT scores of the patients. With decreasing performance (i.e. increasing scores) in the SKT, there was a significant shift in the topographical alpha-centroid towards the left side (r = 0.50, P < 0.05), and of the beta-centroid towards more anterior areas (r = 0.54, P < 0.01).

EEG and HMPAO-SPECT

To investigate the relations between CBF and EEG-frequency bands, the total power and the locations of the topographical centroids of the power bands were correlated with the total brain perfusion (Table 1). After Bonferroni correction, only the more anterior locations of the topographical alpha-centroid were significantly associated with higher total brain perfusion (Fig. 2). Since low

Table 1 Correlations between EEG and cerebral blood flow

	Delta	Theta	Alpha	Beta
Power				
Total perfusion	–0.14	–0.11	0.17	0.40
Centroid: anteroposterior				
Total perfusion	0.10	–0.50	–0.64*	0.09
Centroid: left – right				
Total perfusion	–0.03	0.24	–0.06	–0.18

* P < 0.05 after Bonferroni correction

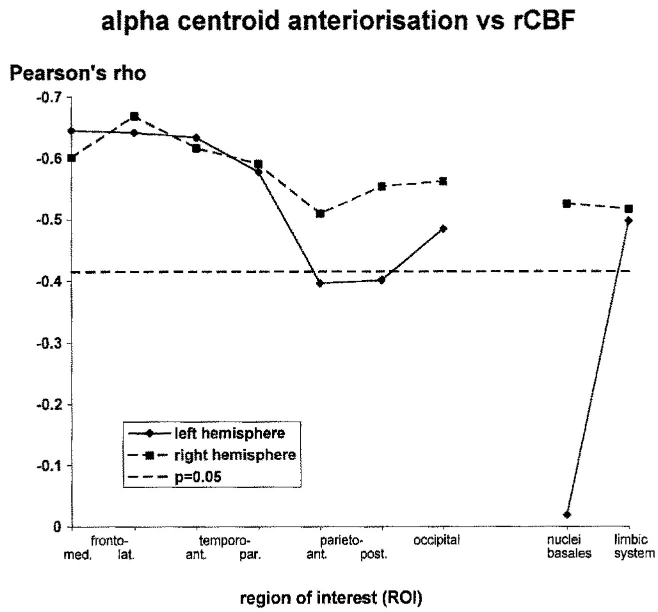

Fig. 2 Correlations between locations of the alpha-centroid on the anterior–posterior axis and rCBF; y-axis: rho-scores; x-axis: ROIs; neocortical structures are separated from nuclei basales and limbic system. The *dashed horizontal line* indicates the uncorrected 5% confidence level

perfusion has been found to be associated with high power in slow frequencies, a correlation matrix was performed for the delta and theta power at the single electrode sites vs perfusion of the ROIs. Only at the left anterior-temporal electrode site were there inverse correlations with the perfusion in the left and right fronto-medial lobe (r = –0.50 and r = –0.47, respectively) and in the left temporal lobe (r = –0.48), significant at the 5% level; however, these significances did not withstand a Bonferroni correction.

Discussion

The major result of the present study was a correlation of the levels of CBF with the locations of the topographical centroids of the power maps. The result of more anteriorly located alpha-centroids being associated with higher CBF was unexpected since both, anteriorisation and reductions in CBF have been described to be progressive in the course of DAT (Maurer and Dierks 1991), and to be linked to clinical severity (Maurer and Dierks 1991; Waldemar et al. 1994).

Although the inverse link between two progressive alterations of the disease cannot be conclusively clarified by this study, two explanations can be hypothesized. Firstly, the anteriorisation of the alpha-centroid which has been found to be typical for DAT (Maurer and Dierks 1987; Chiaramonti et al. 1997; Strik et al. 1997) might follow a U-shaped pattern with anteriorisation in mild and moderate cases, and return to posterior areas in the more severe cases. However, no evidence for this hypothesis was found in the literature and from the psychometric data of the present study. Secondly, different levels of concomitant vascular impairments have been described in DAT (Mann et al. 1994). These vascular lesions may interact with EEG and rCBF in different ways: more pronounced vascular changes presumably enhance rCBF reductions, but might counterbalance DAT-typical topographical EEG changes.

Regarding the relations between EEG power of the slow frequencies and rCBF, Stigsby et al. (1981), Passero et al. (1993) and Kwa et al. (1995) found significant correlations between slowing of the EEG mean frequency and rCBF reductions. In this study correlations of the theta and delta power with rCBF were found at a descriptive level in anterior temporal regions. Since the anatomical locations of these correlations are meaningful in DAT, the result indicates consistent regional effects in both EEG and SPECT, although multiple testing does not allow a confirmatory statement.

As described in previous studies (Soininen et al. 1991a; Schreiter-Gasser et al. 1994), significant correlations between delta and theta power, and the MMSE, were found. Some topographical features of the power maps (left-sided shift of the alpha-centroid, anterior shift of the beta-centroid) were correlated with cognitive impairments in the SKT. Whereas the power of slow frequencies has been shown to be related to clinical severity in previous studies, the topographical features described in this study might add further validity for clinical applications.

Regional CBF levels did not correlate with the clinical scales of the cognitive performance. The link between rCBF and clinical severity has been discussed with controversy. Whereas Maurer et al. (1991) found the cognitive impairment to be related to the degree of blood flow reductions, Montaldi et al. (1990) described less-clear relations between SPECT and the CAMCOG test. Therefore, the latter authors pointed out that clinical scales might produce results which are difficult to interpret in combination with SPECT, since in their study rCBF was related to language and praxia, but not to memory tasks.

In conclusion, the combination of two methods for the investigation of DAT showed that the relationship between the respective typical and progressive alterations was not direct as might have been expected. This indicates that there are differential interactions of the methods with factors which have not yet been considered sufficiently, e.g. with the degree of concomitant vascular lesions. The correlations of SPECT and qEEG with the clinical scales, on the other hand, suggest that the EEG features are more closely related to the functional changes on the basis of the cognitive decline in DAT.

References

Chiaramonti R, Muscas GC, Paganini M, Müller TJ, Fallgatter AJ, Versari A, Strik WK (1997) Correlations of topographical EEG features with clinical severity in mild and moderate dementia of Alzheimer type. Neuropsychobiology (in press)

Dierks T, Perisic I, Frölich L, Ihl R, Maurer K (1991) Topography of the quantitative electroencephalogram in dementia of the Alzheimer type: relation to severity of dementia. Psychiatry Res 40(3): 181–194

Erzigkeit H (1989) The SKT-A short cognitive performance test as an instrument for the assessment of clinical efficacy of cognitive enhancers. In: Bergener M, Reisberg B (eds) Diagnosis and treatment of senile dementia. Springer, Berlin Heidelberg New York, pp 164–174

Folstein M, Folstein S, McHugh PR (1975) Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. Psychiatry Res 12: 189–198

Hachinski VC, Illiff LD, Zilhka E, Du-Boulay GH, McAllister VL, Marshall J, Russell RW, Symon L (1975) Cerebral blood flow in dementia. Arch Neurol 32: 632–637

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23: 56–62

Kwa VI, Weinstein HC, Posthumus-Meyjes EF, van Royen EA, Bour LJ, Verhoeff PN, Ongerboer de Visser BW (1993) Spectral analysis of the EEG and 99m-Tc-HMPAO-SPECT-scan in Alzheimer's disease. Biol Psychiatry 33(2): 100–107

Lehmann D (1987) Principles of spatial analysis. In: Gevins A, Remond A (eds) Handbook of electroencephalography and clinical neurophysiology, vol 1. Methods of analysis of brain electrical and magnetic signals. Elsevier, Amsterdam, pp 309–354

Leuchter AF, Cook IA, Newton TF, Dunkin J, Walter DO, Rosenberg-Thompson S, Lachenbruch PA, Weiner H (1993) Regional differences in brain electrical activity in dementia: use of the spectral power and spectral ratio measures. Electroencephalogr Clin Neurophysiol 87: 385–393

Mann DWA, Neary D, Testa H (1994) Color atlas and text book of adult dementias. Mosby-Wolfe, London

Martin-Loeches M, Gil P, Jimenez F, Exposito FJ, Miguel F, Cacabelos R, Rubia FJ (1991) Topographic maps of brain electrical activity in primary degenerative dementia of the Alzheimer type and multiinfarct dementia. Biol Psychiatry 29(3): 211–223

Maurer K, Dierks T (1987) Brain mapping-topographic demonstration of the EEG and evoked potentials in psychiatry and neurology. EEG. EMG. Z. Elektroenzephalogr Verwandte Geb 18(1): 4–12

Maurer K, Dierks T (1991) Atlas of brain mapping: topographic mapping of EEG and evoked potentials. Spinger, Berlin Heidelberg New York

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer. Neurology 34: 939–944

Montaldi D, Brooks DN, McColl JH, Wyper D, Patterson J, Barron E, McCulloch J (1990) Measurements of regional cerebral blood flow and cognitive performance in Alzheimer's disease. J Neurol Neurosurg Psychiatry 53(1): 33–38

O'Brien JT, Eagger S, Syed GM, Sahakian BJ, Levy R (1992) A study of regional cerebral blood flow and cognitive performance in Alzheimer's disease. J Neurol Neurosurg Psychiatry 55(12): 1182–1187

Passero S, Rocchi R, Vatti G, Burgalassi L, Battistini N (1995) Quantitative EEG mapping, regional cerebral blood flow, and neuropsychological function in Alzheimer's disease. Dementia 6(3): 148–156

Press WH, Teucholsky SA, Vetterling WT, Flannery BP (1993) Numerical recipes in C: the art of scientific computing, 2nd edn. Cambridge University Press, Cambridge

Schreiter-Gasser U, Gasser T, Ziegler P (1994) Quantitative EEG analysis in early onset Alzheimer's disease: correlations with severity, clinical characteristics, visual EEG and CCT. Electroencephalogr Clin Neurophysiol 90(4): 267–272

Sloan EP, Fenton GW, Kennedy NS, MacLennan JM (1994) Neurophysiology and SPECT cerebral blood flow patterns in dementia. Electroencephalogr Clin Neurophysiol 91: 163–170

Soininen H, Partanen J, LaulumaaV, Paakkonen A, Helkala EL, Riekkinen PJ (1991a) Serial EEG in Alzheimer's disease: 3 year follow-up and clinical outcome. Electroencephalogr Clin Neurophysiol 79(5): 342–348

Soininen H, Partanen J, Paakkonen A, Koivisto E, Riekkinen PJ (1991b) Changes in absolute power values of EEG spectra in the follow-up of Alzheimer's disease. Acta Neurol Scand 83(2): 133–136

Stigsby B, Johannesson G, Ingvar DH (1981) Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's diseases. Electroencephalogr Clin Neurophysiol 51(5): 537–547

Strik WK, Lehmann D (1993) Data-determined window size and space-oriented segmentation of spontaneous EEG map series. Electroencephalogr Clin Neurophysiol 87: 169–174

Strik WK, Chiaramonti R, Muscas GC, Paganini M, Müller TJ, Fallgatter AJ, Versari A, Zappoli R (1997) Decreased EEG microstate duration and anteriorisation of the brain electrical fields in mild and moderate dementia of the Alzheimer type. Psychiatry Res (in press)

Waldemar G, Walovitch RC, Andersen AR, Hasselbalch SG, Bigelow R, Joseph JL, Paulson-OB, Lassen NA (1994) 99mTc-bisicate SPECT brain imaging and cognitive impairment in dementia of Alzheimer type: a blinded read of image sets from a multicenter SPECT trial. J Cereb Blood Flow Metab 14: 99–105