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Correlation between cognitive brain function and electrical brain activity in dementia of Alzheimer type

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Summary. Psychometric tests which assess cognitive brain function in dementia disorders are partly prone to artifacts, e.g., the experience of the investigator and the cooperation of the patient influences the results. An objective way to assess the degree of cognitive disturbance could be to measure neuronal activity represented by the electrical brain activity. The aim of the present study was to investigate how well cognitive function in dementia assessed by psychometric tests correlates with electrical brain activity (EEG). Multichannel EEG data was reduced into 3-D intracerebral equivalent dipole EEG generators allowing a more convenient statistical data management and valid physiological data interpretation. 35 patients suffering from dementia of Alzheimer type were investigated. An increase of dipole strength in the slow frequency bands, a more anterior equivalent dipole of alpha- and beta-activity, and a slowing of the EEG with increasing cognitive deterioration could be demonstrated. The results support the hypothesis that the amount of disturbance of cognitive function in dementia can be assessed by measuring the electrical activity of the brain.

Keywords: Dementia of Alzheimer Type, EEG, cognitive function, FFT-approximation, dipole estimation

Introduction

Various test instruments to assess cognitive function in dementia have been developed in recent years. Some of these instruments are psychometric tests which measure the cognitive function more globally (e.g., mini-mental-state-examination MMSE; Folstein et al., 1975, or the global deterioration score, GDS; Reisberg et al., 1983), others are intended to measure the cognitive function in dementia in greater detail (e.g., Brief Cognitive Rating Scale, BCRS; Reisberg et al., 1983, or Alzheimer's disease Assessment Scale, ADAS; Mohs and Cohen, 1988). Although being validated using standard psy-

chometric criteria, these tests are obviously not entirely objective, since the results to a certain degree depend on factors like patient cooperation or the experience of the investigator. A more objective way to assess brain function in dementia is to measure the electrical brain activity.

Ever since the German psychiatrist Hans Berger measured the human EEG in 1924 (Berger, 1929) clinicians as well as researchers have attempted to conceptualize electrical activity of the brain (neuronal activity) as a reflection of mental processes. Cognitive processing is a part of mental processes and, if reflected in the EEG, a correlation between cognitive psychometric tests and EEG features may possibly exist.

Due to recent advances in computer software and hardware it is now possible to sample electrical information from the brain with high temporal and relatively high spatial resolution. However, the increasing amount of data make a sensible interpretation of the data increasingly complicated. One way to reduce data in a reasonable way is to calculate equivalent dipoles, which describe the electrical activity of the brain as one or more dipoles generating the electrical field over the surface of the scalp. The calculation of dipoles has mostly been accomplished in the time domain, for e.g., epileptic discharges in the EEG or for evoked potentials. For the investigation of continuous (not task related) mental processes or cognition, however, the analysis of the background EEG (frequency domain) is of higher interest than an analysis of episodic EEG features in the time domain.

Lehmann and Michel (1989) recently presented the FFT-approximation as a simple and elegant method to calculate equivalent dipoles of frequency components of EEG. The FFT-approximation allows an estimation of the intracranial representation of mental processes of the brain, which generate the electrical fields measured upon the scalp. These equivalent dipoles are independent of the choice of reference.

The aim of the present investigation was thus to elucidate if a correlation exists between psychometric test results and electrical activity of the brain as described by equivalent dipoles in the frequency domain in patients with cognitive impairment and which EEG features may be sensitive to alterations in cognition.

Methods

We studied 35 patients suffering from probable DAT (19 women, 16 men, mean age [± standard deviation] 69 ± 11 years, age range from 42 to 83 years) in various stages of mental impairment. All patients were right-handed and only those who were not taking drugs influencing cerebral functions for at least 14 days were included in the study. All patients fulfilled the criteria for probable DAT (McKhan et al., 1984). They were hospitalized for a period of 2–3 weeks for diagnostic evaluation. Diagnostic assessment included history, physical and neurological examination and routine laboratory tests (incl. thyroid hormone levels and Vitamine B12 and folate). The modified Hachinski ischemic score (score < 4) (Rosen et al., 1984) was used to exclude multi-infarct dementia. Further selection was based on CT scans in all patients which showed only cerebral atrophy, ventricular dilatation and no more than 1 lacunar infarction, if abnormal. In no case, there were territorial infarctions. In most patients, single photon emission computed tomography

with Tc-99 m-hexamethylpropylene-amine-oxime (HMPAO-SPECT) was performed and did not reveal signs of multifocal flow deficits. Typically, temporo/parietal and/or frontal flow deficits were found (Froelich et al., 1989). All patients were investigated with a battery of neuropsychological tests for cognitive function, language, apraxia, agnosia, visospatial abilities, mood, and behavioral changes. The stage of mental impairment was assessed by means of Mini-Mental-Status-Examination (MMSE; Folstein et al., 1975), the Brief Cognitive Rating Scale (BCRS; Reisberg et al., 1983), the Short Syndrome Test (SKT; Erzigkeit, 1989), and the Alzheimer's disease assessment scale (ADAS; Mohs and Cohen, 1988). All tests except the MMSE lead to higher scores with decreasing cognitive function, the MMSE leads to lower scores with decreasing cognitive ability.

Data acquisition

Silver-silver chloride cup electrodes were applied at 20 sites to the scalp according to the international 10–20 system (Fpl, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, and O2). The EEGs were recorded referred to linked mastoids. The recording localizations on the scalp were cleaned to ensure low impedances and the electrodes were fastened by paste. Prior to the recording the impedances were measured, and low and similar values were ensured in all channels (in each channel lower than 3 kOhm and interelectrode difference lower than 1 kOhm). The subjects were lying comfortably on a bed. Data were recorded with a 20 channel Bio-Logic Brain Atlas III Plus. The EEG was sampled with a rate of 128 Hz per channel and stored onto magnetic disks for further analysis off-line. Before AD-conversion the EEG was analog-filtered with a band pass of 1.0–30.0 Hz. Overall amplification was 20.000 times. For data analysis the first five successive artifact free 2 sec epochs, starting 20 sec after eyes were closed, were selected off-line from the stored EEG. For all subjects 5 artifact-free successive epochs could be gained.

Data processing

Fast Fourier analysis was done on each 2 sec epoch, multiplied with a Hamming window. The resulting sine and cosine coefficients for each electrode and for each frequency point were placed into a sine-cosine diagram (Lehmann et al., 1986). When a single-generator model is supposed to explain such data, the generated field has to meet two conditions a) all phase angles between recording electrodes are either 0° or 180°, and b) the spatial distribution of the amplitudes conforms to a single-dipole configuration. Since recorded FFT-data in general show an ellipsoid configuration of entries, their phase angles and amplitudes deviate from the single dipole case. The observed phase-angles are approximated by a least-deviation set of 0° and 180° phase angles. To achieve this approximation all entries in the diagram have to be orthogonally projected upon a "best-fit" line running through the data. The projection of the FFT-constellation on the best-fit line is called "FFT-approximation" (Lehmann and Michel, 1989) and describes a map of potential distribution, which is used for estimation of the equivalent dipole source which gives the least-deviation set of dipole-field amplitudes. For a detailed description and discussion of this method see Lehmann and Michel (1989, 1990) and Dierks et al. (1993).

For equivalent-dipole source localization we used a moving dipole model (Kavanagh et al., 1978) for each frequency point in the FFT approximation, and thus for each frequency a "center of gravity" localization for the generating electrical sources was calculated with four resulting parameters a) magnitude (μV), b) right-left (mm) localization, c) anterior-posterior (mm), and d) superior-inferior (depth) localization (mm) of the equivalent-dipole. The fit for one single dipole was computed by the program BESA using the moving dipole solution. The two parameters describing the direction of the dipole were not used since the polarity of the potential distribution map depends on the position of the best-fit line in the sine-cosine diagram. However, the polarity does not influence the result-

Table 1. Correlation coefficients between **a** intensity of the equivalent dipole, **b** localization in left-right direction, **c** localization in anterior-posterior direction and **d** localization in superior-inferior direction (depth) of the equivalent dipole and psychometric test results for the delta (1.0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–11.5 Hz), beta 1 (12.0–15.5 Hz), beta 2 (16.0–19.5 Hz), and beta 3 band (20.0–23.5 Hz) (*BCRS* Brief Cognitive Rating Scale, *SST* Short Syndrome Test, *MMSE* Mini Mental Status Examination, *ADAS* Alzheimer Disease Assessment Scale) (* = $p < 0.05$, ** = $p < 0.01$)

Table 1 a

	Delta	Theta	Alpha	Beta 1	Beta 2	Beta 3
BCRS	0,15	0,26	–0,36*	–0,22	–0,27	–0,22
SST	0,34*	0,47**	–0,19	–0,1	–0,06	–0,07
MMSE	–0,27	–0,26	0,37*	0,18	–0,21	0,19
ADAS	0,35*	0,47**	–0,24	–0,17	–0,25	–0,26

Table 1 b

	Delta	Theta	Alpha	Beta 1	Beta 2	Beta 3
BCRS	–0,18	–0,12	0,04	0,07	0,03	0,02
SST	–0,09	0,03	0,08	0,07	0,11	–0,03
MMSE	0,10	0,11	–0,05	–0,03	–0,01	0,06
ADAS	0,01	0,07	0,19	0,13	0,09	–0,10

Table 1 c

	Delta	Theta	Alpha	Beta 1	Beta 2	Beta 3
BCRS	–0,03	0,01	0,24	0,31	0,2	0,19
SST	–0,01	–0,09	0,28	0,47**	0,25	0,32
MMSE	–0,04	0,01	–0,23	–0,46*	–0,35*	–0,35*
ADAS	0,05	–0,09	0,33*	0,43*	0,15	0,24

Table 1 d

	Delta	Theta	Alpha	Beta 1	Beta 2	Beta 3
BRCS	0,12	0,11	0,13	0,29	0,25	0,17
SST	–0,03	0,01	0,14	0,24	0,17	0,11
MMSE	–0,16	–0,19	0,21	–0,32	–0,26	–0,18
ADAS	0,2	0,10	0,24	0,24	0,21	0,11

ing dipole localization (Lehmann and Michel, 1990). The localizations were expressed as distance from the middle point of a spherical head model (zero value; 10% level in the 10–20 system).

Finally the 5 gained 2 sec epochs for each subjects were averaged and used for further statistical processing

.Statistical analysis

The data of the localization of equivalent-dipoles in the patients and the psychometric test results followed a normal distribution (Kolmogoroff-Smirnoff-test), entitling the use of the parametric Pearson linear correlation for an exploratory analysis of the relation between EEG and psychometric variables.

Results

For each subject the frequency was calculated at which the equivalent dipole reached its maximum (peak frequency). There was a significant correlation between peak frequency and cognitive decline (e.g., with BCRS $r = 0.41$; $p < 0.01$). The intensity of the activity in the slow frequency bands correlated positively with increasing cognitive decline measured by ADAS and SKT, that is with increasing cognitive deficits the delta and theta activity increased (Table 1 a). However, no correlation could be observed between delta and theta activity and cognitive decline when using the MMSE and the BCRS for assessing cognitive function.

An opposite effect could be seen regarding the alpha intensity, where an increasing cognitive impairment measured by the MMSE and BCRS correlated with a decrease of strength, whereas the ADAS and SKT did not show such a correlation.

In left-right direction no significant correlation between psychometric test results and localization of the equivalent dipoles could be observed (Table 1 b).

In anterior-posterior direction neither the delta band nor the theta band showed a significant correlation with any psychometric scale. On the other hand, the alpha and the beta bands demonstrated a positive correlation between severity of cognitive decline and anterior localization of the equivalent dipole (Table 1 c). Whereas in the alpha band only the ADAS demonstrated this correlation, in the beta 1 band SKT, MMSE and ADAS score correlated significantly with localization of the equivalent dipole in anterior-posterior direction. In the beta 2 and beta 3 band only the MMSE correlated with localization in anterior-posterior direction (Table 1 c).

Concerning the depth of the equivalent dipole no significant correlations were encountered, only the beta bands showed a tendency that with decreased cognitive capability the dipoles were more superficially localized (Table 1 d).

Discussion

Summarizing the present investigation, we demonstrated a) an increase of dipole strength in the slow frequency bands, b) a more anterior equivalent dipole of alpha- and beta-activity, and c) a slowing of the EEG with increasing cognitive deterioration. The results support the assumption that cognitive decline in dementia can be assessed by measuring the electrical activity of the brain.

Our results regarding the strength of a dipole may be compared to studies

dipole of alpha- and beta-activity, and c) a slowing of the EEG with increasing cognitive deterioration. The results support the assumption that cognitive decline in dementia can be assessed by measuring the electrical activity of the brain.

Our results regarding the strength of a dipole may be compared to studies which have investigated the activity of frequency-bands with the help of conventional FFT results. A number of investigations have described increased slow wave activity with increasing cognitive deterioration (Coben et al., 1985; Penttilä et al., 1985; Brenner et al., 1986). This is analogous to our finding of a positive correlation between equivalent dipole strength in the theta band and mental deterioration. For the alpha band several authors have described decreased activity with increasing cognitive decline, comparable to our finding of reduced intensity in the alpha band with decreasing cognitive function (Letemendia and Pampligione, 1958; Gordon and Sim, 1967; Saletu et al., 1991).

In geriatric depression we have found similar results as in early stages of dementia of Alzheimer type, making a differential diagnosis by the use of EEG between the diseases difficult (Dierks et al., 1993). Aging itself does not lead to findings similar to those reported in this study. Most investigations regarding the influence of aging on EEG parameters have been negative when only including subjects with full cognitive functioning, verified by psychometric tests. The specifity of the present findings are, however, of less importance since the result suggests that the EEG may be used for staging of dementia after the diagnosis has been confirmed.

Studies investigating topographical changes of electrical activity in relation to severity of cognitive deterioration are few. Breslau et al. (1989) reported a change towards increased beta activity over central regions in aged normals compared to younger ones, but did not comment on findings in their DAT population with cognitive impairment. Ihl et al. (1989) found a stage-dependent decrease of beta activity in temporo-parietal regions. In our own study in which we investigated the topography of the peak frequency, we found a clear anteriorization of the peak frequency in demented patients, however, no correlation was found between anteriorizing of peak frequency and degree of dementia (Dierks et al., 1991). Our finding of anteriorization of the beta dipole in DAT patients may be interpreted as an increased vulnerability of parieto-temporal and occipital regions, with normal beta activity maintained in frontal regions for a longer duration. Significant correlations between the localization of the equivalent dipole of the alpha band in anterior direction and neuropsychological testing, also reported for conventional alpha activity in occipital region and 'Mini-Mental-State' by Primavera et al. (1990), support this hypothesis.

The reason for the variability in correlation between psychometric and EEG parameters may be seen in a) the subjectivity when performing the test and b) in the different sensitivity of the different psychometric tests in the various stages of cognitive deterioration. Whereas e.g., SKT is more sensitive in mild

to moderate degree of cognitive dysfunction MMSE is rather insensitive to mild degree of cognitive impairment (Ihl et al., 1992).

The strength in the FFT approximation lies in its ability to reduce multichannel data into few parameters, which allow a separate confirmative conservative statistical evaluation of intensity of EEG activity and topographical distribution either between patient groups or in relation to other clinical or laboratory data. It has to be kept in mind that the resulting single equivalent dipole does not show the exact localization of anatomical structures which are generating the surface potential. It should be considered as the sum of all neuronal processes which are simultaneously active and are generating the potential measured upon the scalp. Nevertheless, differences in localization of the calculated single equivalent dipole allow the conclusion that different localized neuronal structures have been active (Michel et al., 1992).

Furthermore, the use of one single dipole has several advantages, firstly with regard to data-reduction and statistical handling of the data. Secondly regarding physiological interpretation: the use of several dipoles makes it necessary to constrain the dipole model to a higher degree as compared to the use of one single dipole to reduce the degrees of freedom. The choice of different constraints may lead to different results. In the present study we wanted to avoid this and as much as possible use a data-driven model and not one that depends on the choice of limitations put on the model.

The clinical advantages of the present method are, as for the EEG, obvious: non-invasiveness, ease of measurement, possibility of follow-up and cheapness. Thus, a tool for a sensible objective quantification of cognitive impairment in patients with Alzheimer's disease may be available.

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