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Depth of word processing in Alzheimer patients and normal controls: a magnetoencephalographic (MEG) study

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Summary. Effects related to depth of verbal information processing were investigated in probable Alzheimer's disease patients (AD) and age matched controls. During word encoding sessions 10 patients and 10 controls had either to decide whether the letter ''s'' appeared in visually presented words (alphabetical decision, shallow encoding), or whether the meaning of each presented word was animate or inanimate (lexical decision, deep encoding). These encoding sessions were followed by test sessions during which all previously encoded words were presented again together with the same number of new words. The task was then to discriminate between repeated and new words. Magnetic field changes related to brain activity were recorded with a whole cortex MEG.

5 probable AD patients showed recognition performances above chance level related to both depths of information processing. Those patients and 5 age matched controls were then further analysed. Recognition performance was poorer in probable AD patients compared to controls for both levels of processing. However, in both groups deep encoding led to a higher recognition performance than shallow encoding. We therefore conclude that the performance reduction in the patient group was independent of depth of processing. Reaction times related to false alarms differed between patients and controls after deep encoding which perhaps could already be used for supporting an early diagnosis.

The analysis of the physiological data revealed significant differences between correctly recognised repetitions and correctly classified new words (old/new-effect) in the control group which were missing in the patient group after deep encoding. The lack of such an effect in the patient group is interpreted as being due to the respective neuropathology related to probable AD. The present results demonstrate that magnetic field recordings represent a useful tool to physiologically distinguish between probable AD and age matched controls.

Keywords: Alzheimer, word processing, MEG, early diagnosis.

1. Introduction

A major reason for investigating the brain mechanisms that underlie behaviour is not only to understand normal brain functions, but also to have a basis for understanding and treating medical disorders of the brain. Facing that idea the present study was meant to contribute to the understanding of the Alzheimer's disease (AD).

According to Braak and Braak (1995) the AD is neuropathologically characterised by neurofibrillary tangles and senile plaques. They have described six stages of disease propagation with respect to the location of tangle-bearing neurons which are initially located within medio-temporal limbic structures and then spread out to neocortical association areas (see also Lewis et al., 1987; De Lacoste et al., 1993; Morrison and Hof, 1997; Golob et al., 2001).

Consequently, during the course of disease propagation a chronological series of functional impairments is to be expected. The neuropsychological profile usually comprises severe anterograde amnesic syndrome due to early hippocampal neuropathology followed by impairments related to a number of higher cognitive functions which depend on neocortical association activities. For example, within a visual prototype learning task recognition was impaired in patients with mild AD (Mini-Mental score 18–23) and moderate AD (Mini-Mental score <18). On the other hand, categorisation was impaired only in patients with moderate AD (Keri et al., 2001). The authors suggested that while the medio-temporal/diencephalic explicit memory system is markedly affected even in early AD, the sensory neocortical areas mediating implicit category learning display a sufficient degree of functional capacity until later stages of the disease.

The focus of the present study was to determine psychological and physiological effects related to depth of verbal information processing and following recognition performance in probable AD patients compared to controls. In particular, brain activity was recorded during recognition performances related to shallow and deep word encoding in both groups. As mentioned above the impairment of implicit processes is a consequence of moderate AD including later stages of disease propagation whereas mainly explicit processes are impaired at early stages. Due to the idea that the recognition of deep encoded words depends on explicit memory functions to a higher degree than the recognition of shallow encoded words it is expected that shallow encoding is not as affected as deep encoding related to probable AD. Differences between probable AD patients and controls are expected to predominantly occur in relation to deep encoding.

Shallow and deep word encoding, in other words ''depth of word processing'' has an influence on subsequent recognition performance (Craik and Lockhart, 1972). This finding can be interpreted as evidence reflecting different engagement of implicit and explicit processes related to shallow and deep word encoding. Also physiological evidence has been reported distinguishing between brain processes that underlie different depths of verbal information processing. The deeper a word is processed the better it is subsequently recognized and the higher is its brain activity as has been recently shown within a

magnetoencephalographic (MEG) study (Walla et al., 2001). It has also been suggested that the activity of the left prefrontal cortex is modulated as a function of encoding operations using the electroencephalography (EEG) (Lang et al., 1988) and the positron emission tomography (PET) (Kapur et al., 1994). Variable olfactory influences on verbal information processing depending on depth of word processing have been described (Walla et al., 2003). Thus, the controlled modulation of depth of information processing proved to be a reliable approach for various kinds of investigations.

The differential involvement of implicit and/or explicit processes is one key point, another important previous finding is the so called old/new event-related potential (ERP) effect. This effect describes physiological differences between correctly recognised repeated words and correctly judged new words (e.g. Paller and Kutas, 1992; Rugg, 1995; Allan and Rugg, 1997; Allan et al., 1998). Correctly recognized repetitions produce more positive-going waveforms than correctly judged new words mostly at temporo-parietal electrode sites starting from around 300–400 ms after stimulus onset and persisting for about 600–1000 ms (e.g. Rugg and Doyle, 1992). Recently, the first magnetoencephalographic (MEG) study was conducted to investigate the old/new effect in normal young study participants (Tendolkar et al., 2000). The respective MEG results showed physiological differences between both classes of words in the range of 400 ms to 1000 ms after stimulus onset. Since the temporal resolution of both methods is in the range of milliseconds these similar results are not surprising.

The goal of the present study was to use the MEG to investigate the old/new effect in a group of probable AD patients in comparison to a group of normal controls by providing two levels of word processing. It was intended to determine whether probable AD patients demonstrate selective effects depending on depth of word processing on both a physiological and a psychological level. The MEG is an electrophysiological method providing a high temporal resolution in the range of milliseconds and therefore allows an excellent description of the dynamics of brain processes (Hari, 1991).

Not at least, our approach might also represent an interesting contribution to an early diagnosis of the AD.

2. Methods

2.1 Participants

10 probable AD patients (1 female) participated in the present study and gave their informed consent. They had no history of vascular events and sufficient seeing ability to read the visually presented words without wearing glasses. The mean age was 75.4 (SD = 5.5). The mean Mini Mental State Examination (Folstein et al., 1975) score was 23 (SD = 1.4). All patients were subjected to a battery of neuropsychological tests that included measures of concentration/attention, language and memory. The Alters-Konzentrations-Test (AKT) (Gatterer, 1990) a geriatric cancellation test and the digit symbol subtest of the German WAIS-R were applied to assess the capacity for concentration and attention. Semantic verbal fluency (1 min animals test) and phonematic verbal fluency (COWA) were also assessed (Lezak, 1995). Verbal and nonverbal short term memory were assessed by using the digit span and Corsi block tapping (Lezak, 1995). In order to test episodic memory the Memory Assessment Clinics (MAC) battery was used. For the present study the Austrian version of the MAC using the subtests Selective Reminding total

recall, Selective Reminding delayed recall and Recognition of Faces – Delayed non-matching to sample were used (Crook et al., 1986). After the completion of the evaluation a consensus committee meeting was held involving the neurologist, neuropsychologists and other study personnel who had evaluated the patients. Diagnosis for dementia were made according to DSM-III-R (American Psychiatric Association, 1987). Probable AD was defined according to the National Institute of Neurological and Communication Disorders Association Criteria (McKahnn et al., 1984).

The mean age of the subgroup of patients (5 men) who exhibited recognition performances above chance level was 73 years (SD = 5.5). Their mean Mini Mental State Examination score was 23 (SD = 1.41).

5 healthy participants (4 females) formed the control group for the comparison with the early AD patients. The mean age of this group was 72.8 (SD = 6.1). Their mean Mini Mental State Examination score was 29.5 (SD = 0.71).

A oneway ANOVA revealed a significant group effect (patients/controls) related to the Mini Mental State Examination Score ($p = .004$) and a not significant group effect related to age ($p = .958$). These data confirm the validity of both groups for a comparison. The factor gender was not matched between groups (AD patients consisted of men only whereas in the control group 80% of study participants were female) and no between group statistical analysis was calculated with physiological data. Instead, we focused on within group analysis investigating the old/new effect for each group separately. The factor gender is not important for the present study because in normal healthy people both males and females demonstrate a reliable old/new effect (e.g. Allan and Rugg, 1997; Allan et al., 1998; Tendolkar et al., 2000).

Therefore, any abnormality is related to the AD rather than the different ratio of male and female participants in both groups.

2.2 Procedure

All participants, patients and controls, were seated on a comfortable chair and viewed a screen in front of them onto which words were visually presented (distance from eyes to screen was around 1.70 m and the visual angle for words was between 1.5° and 3.6°). Each word appeared for 500 ms with an inter stimulus interval of 2.5 s. Before the presentation of each word a plus (+) was shown as a fixation point. In total, 888 German nouns (3 to 9 letters for the original word list see Walla, 1998) were shown during one experiment which consisted of four sessions each session consisted of a study phase (74 words) and a test phase (148 words). During two study phases the participants were instructed to decide whether the letter "s" occurred in each presented word or not. This kind of word encoding is referred to as "shallow". During the remaining two study phases they were instructed to decide whether each words meaning was animate or inanimate. This kind of word encoding is referred to as "deep". After each study phase a separate test phase during which all corresponding study words were shown again together with the same number of new words followed. The participants then had to discriminate between previously presented and new words.

In all cases the participants responded by pressing one of two keys. One key was for the left hand and the other one was for the right hand. Response hand, the arrangement of shallow and deep encoding sessions and the lists of stimulus words were counterbalanced between participants.

2.3 Recordings

The MEG was a 143 channel whole-head-system manufactured by CTF Systems Inc. (Canada). The sampling rate was 250/s and recordings were filtered online with a bandpass from 0.25 to 80 Hz. An offline bandpass filter from 0.3–30 Hz was applied. The offline digital filters were zero phase filters (CTF Systems Inc.) in order to minimalize amplitude changes related to filtering. Average event-related fields (ERFs) were calculated for every single participant and across all participants (within each group) who showed a recognition performance above chance level for each encoding condition. The coordinates of the MEG data sets based on the nasion and the left and right preauricular points of the participants in relation to the sensor locations (individual coordinate systems). Intra individual head positions were not changed between experimental

blocks and inter individual differences were kept as small as possible. Magnetic field maps were created to visualize the magnetic field distributions related to the relevant conditions. Difference maps were made in order to show the distributions of activity differences.

2.4 Statistics

2.4.1 Behavioral data

First, the present set of behavioral data consists of 4 relevant conditions which are "hits" (correctly recognised repeated words), "misses" (repeated words which are not recognised), "correct rejections" (correctly judged new words) and "false alarms" (new words which are wrongly classified as repeated). In addition, reaction times to all those 4 conditions are provided. A Repeated Measures Design was used to calculate behavioral between group effects related to all conditions. A Repeated Measures Design was also used to calculate any effects related to reaction times. In addition, paired t-tests were calculated to compare the means of reaction times and performance accuracies.

2.4.2 Physiological data

In order to analyze statistically any activity differences between the relevant test conditions within both groups the mean amplitudes of 100 ms intervals (overlapping for 50 ms) covering the time range from 0 ms to 800 ms after stimulus onset were determined for each condition, each sensor and every single participant. Although the actual sampling rate was 250 per second we averaged data points across 100 ms intervals in order to reduce the number of variables. Analysis of Variance (ANOVA; Repeated Measures Design) where these mean amplitudes were dependent variables were calculated to test interactions between test conditions and sensor locations (All data were Huynh-Feldt corrected). For these calculations a set of 60 sensors was chosen out of the total of 143 sensors in order to reduce the number of variables (Fig. 1). These 60 sensors represent 4 regions on the head surface, namely left frontal, right frontal, left parietal and right parietal. This selection is based on the respective MEG maps of the present study as well as on previous experience in various similar studies. A temporal neural generator for example (as it is often seen)

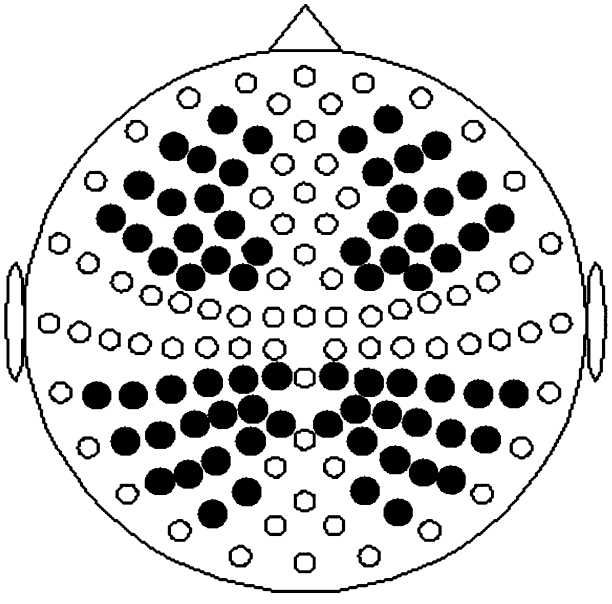


Fig. 1. Distribution of selected sensors of interest in order to reduce the number of variables for the Analysis of Variance (ANOVA)

produces a frontal and a parietal maximum (ingoing and outcoming magnetic field). For showing the distribution of significant effects t-tests were calculated for all sensor locations. Significant effects were marked at the respective sensor locations and plotted on a two dimensional sensor distribution map.

3. Results

3.1 Behaviour

3.1.1 Recognition performance related to shallow and deep encoding

From a total of 10 probable AD patients (1 female) 5 patients (0 female) showed detectable word recognition performances whereas the others performed at chance level. Strikingly, these 5 patients also showed a significant difference in recognition performance related to prior depth of word processing. The mean recognition performance (corrected for guessing) after shallow encoding was 7.8% (SD = 3.8) and the mean recognition performance (corrected for guessing) after deep encoding was 17.8% (SD = 8.6) (Fig. 2). The difference of 10% is significant as calculated by a paired t-test ($p = .013$; $T = 4.27$).

All 5 controls showed detectable recognition performances. The mean recognition performance (corrected for guessing) after shallow encoding was 22.4% (SD = 7.1) and the mean recognition performance (corrected for guessing) after deep encoding was 44.7% (SD = 18) (Fig. 2). The difference of 22.3% is significant as calculated by a paired t-test ($p = .049$; $T = 2.79$).

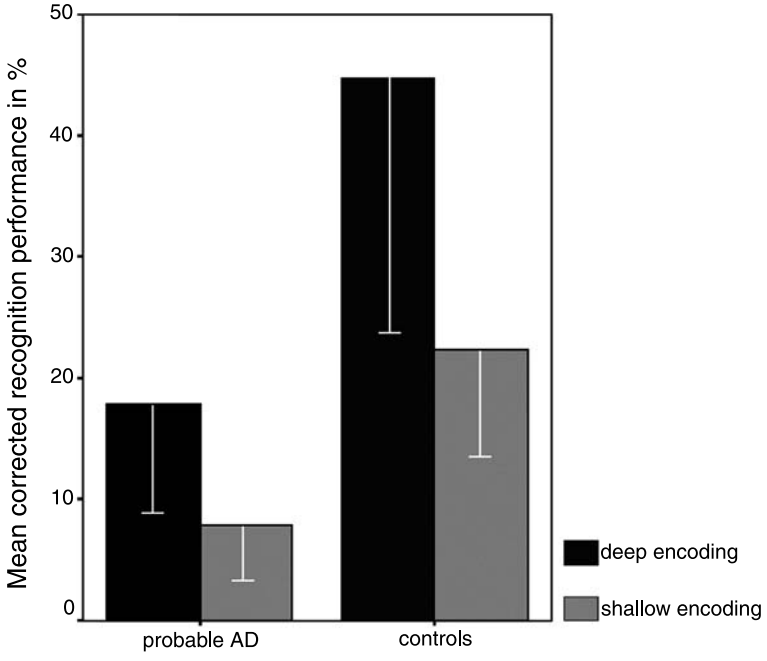


Fig. 2. Mean corrected recognition performances for early AD patients and controls related to both depth of verbal information processing. Note that early AD patients showed reduced recognition performances compared to controls, whereby also in AD patients deep encoding led to a higher performance than shallow encoding

Table 1a. Individual recognition performances (corrected for guessing) for every single AD patient and every single control participant. Note that in both groups every single participant demonstrates a better recognition performance after deep encoding. Note also that related to both levels of processing control participants demonstrated better recognition performance than AD patients. Please, see Fig. 1 presenting bars showing average results

		P1	P2	P3	P4	P5
AD patients	Deep encoding	9.5	15.6	16.2	15.5	32.5
	Shallow encoding	3.4	6	6.8	9.4	13.5
Controls	Deep encoding	54	23	56.7	27.7	62.2
	Shallow encoding	32.4	22.3	13.5	18.3	25.6

Table 1b. Individual reaction times related to all conditions for every single AD patient and for every single control participant. Note that reaction times related to false alarms after deep encoding are obviously shorter in AD patients compared to control participants. Please, see Fig. 2 presenting bars showing average results

		Hit-deep	Hit-shallow	Miss-deep	Miss-shallow	Corr. Rej.-deep	Corr. Rej.-shallow	False alarm-deep	False alarm-shallow
AD patients	P1	1247.7	1176.8	1313.3	1260.7	1281.5	1173.6	1186.7	1255.1
	P2	954.8	757.5	1115.9	920.7	1089.8	828.3	1089.7	877.1
	P3	840	1185.7	1171.3	1241.7	1079.1	1275.4	784.5	1229.8
	P4	1309.3	1328.8	1118.9	1116.6	1126.8	1163.2	1310.6	1302.4
	P5	1085.6	1140	1145.2	1036.8	1092.2	1075.7	1147.6	1151.9
Controls	P1	847.7	864.3	922.9	952.9	843	867.3	910.7	1020.4
	P2	1242	1170.8	1035.7	1005	1056.9	1025.6	1319.5	1203.2
	P3	1004.9	1047.4	1008.4	892.7	1001.1	908	1096.1	1038.6
	P4	1102.9	1125.5	1068.2	1215.6	1072.9	1166.6	1411.3	1211.1
	P5	1216.3	1274	1289.8	1287.1	1191.8	1226.2	1427.9	1348.3

A repeated measures design with "*depth*" as inner subject factor and "*group*" as between subject factor revealed a significant "*depth*" effect ($F = 15.085$; $p = .005$) and a not significant "*depth* $*$ *group*" interaction ($F = 2.178$; $p = .178$). These results underline that in both groups depth of processing had a similar effect on subsequent memory performance. Table 1 provides the values related to every single participant.

3.1.2 Reaction times related to recognition performances (after shallow and deep encoding)

The reaction times related to all classes of words (hits, misses, correct rejections and false alarms) from the recognition tests (shallow encoding and deep encoding) for both the probable AD patients and the control group can be seen in Fig. 3. An Analysis of Variance revealed an almost significant interaction of word-class $*$ depth of processing $*$ group ($F = 2.738$; $p = .090$, Huynh-Feldt corrected) pointing to an interesting trend. In the control group the general pattern of reaction times was similar between both depths of processing. Both after shallow and

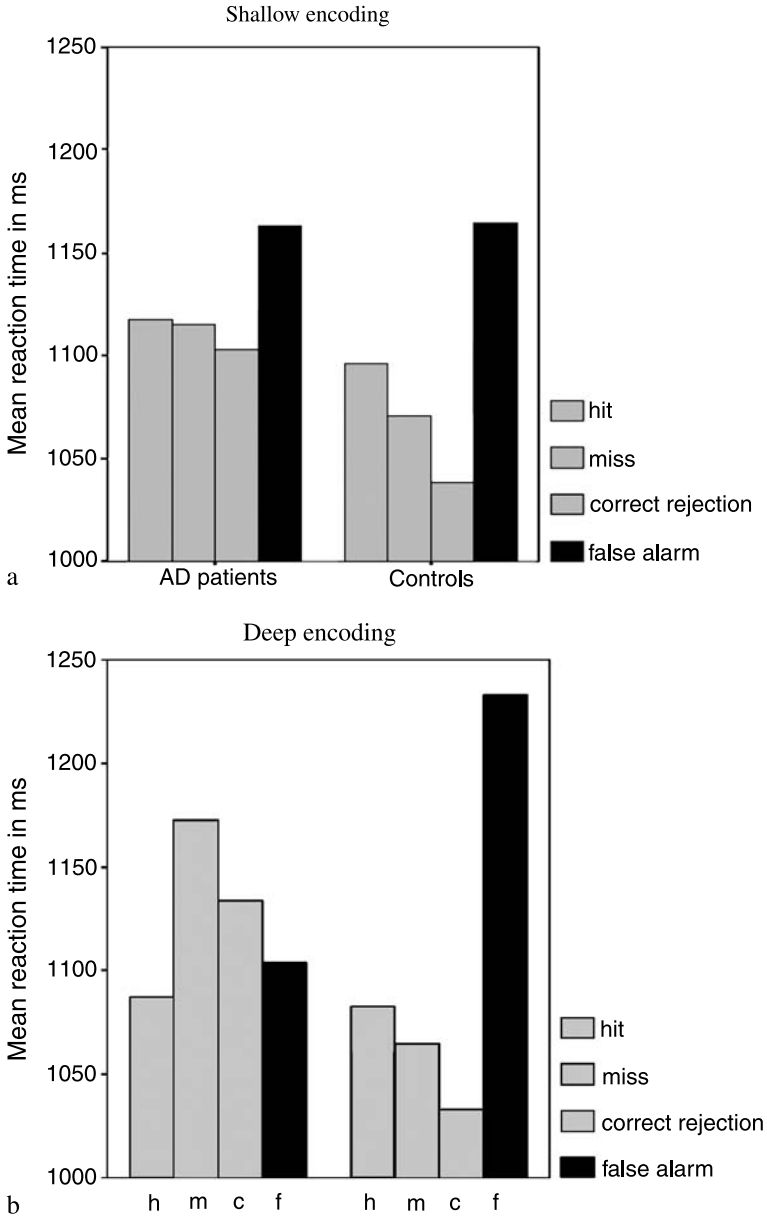


Fig. 3. Mean reaction times related to all word conditions from the recognition test phases. **a** Shallow encoding: The pattern of reaction times is markedly similar between early AD patients and controls, false alarms being associated with longest times. **b** Deep encoding: As can be seen after deep encoding reaction times related to false alarms are reduced compared to the other conditions in early AD patients whereas the pattern of reaction times in controls is very similar to that after shallow encoding

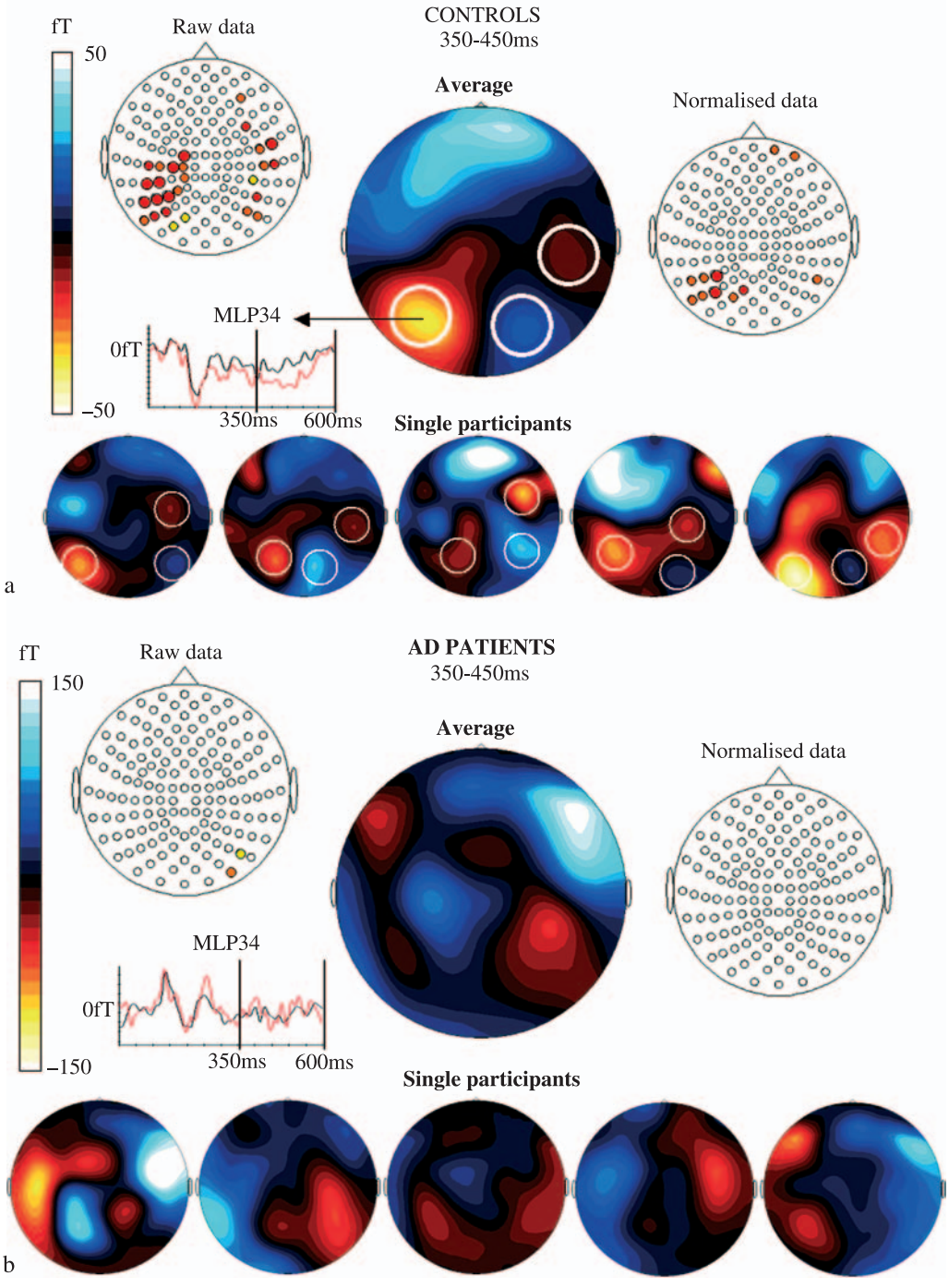
deep encoding reaction times related to false alarms were significantly longer than those related to correct rejections ($p = .005$, $T = -5.595$ for shallow encoding; $p = .018$, $T = -3.888$ for deep encoding). In probable AD patients the pattern of reaction times after shallow encoding was quite similar to normal controls. False alarms were associated with longer reaction times than correct

Table 2. ANOVA results of raw data for controls and early AD patients and for deep and shallow encoding: P-values of cond main effects and *cond * sens* interactions are displayed for consecutive 100 ms time intervals (overlapping for 50 ms). Significant values are bold

Interval	0–100	50–150	100–200	150–250	200–300	250–350	300–400	350–450	400–500	450–550	500–600	550–650	600–700	650–750	700–800
Controls															
Deep encoding/old-new effect/raw data															
cond	F = 244	F = 1.286	F = 1.166	F = 1.588	F = 4.290	**F = 10.74**	F = 1.020	F = 1.752	F = .026	F = .049	F = .000	F = 1.150	F = 5.076	F = .129	F = 1.195
	p = .647	p = .320	p = .341	p = .276	p = .107	**p = .031**	p = .370	p = .256	p = .880	p = .836	p = .991	p = .344	p = .087	p = .129	p = .336
Cond/	F = 1.145	F = 1.331	F = 1.148	F = 1.587	**F = 1.916**	**F = 1.944**	**F = 2.373**	**F = 3.653**	**F = 2.770**	F = 1.643	F = 1.635	F = 1.260	F = .894	F = .902	F = 1.374
sens	p = .324	p = .197	p = .357	p = .109	**p = .023**	**p = .001**	**p = .003**	**p = .002**	**p = .039**	p = .175	p = .148	p = .297	p = .546	p = .513	p = .278
Controls															
Shallow encoding/old-new effect/raw data															
cond	F = 1.728	F = .494	F = 3.233	F = 7.186	**F = 23.5**	**F = 17.3**	F = 2.657	**F = 8.12**	**F = 11.5**	**F = 44.7**	**F = 27.1**	F = 6.844	**F = 9.19**	**F = 7.80**	F = 1.013
	p = .259	p = .494	p = .147	p = .055	**6p = .008**	**5p = .014**	p = .178	**0p = .046**	**3p = .027**	**1p = .003**	**6p = .006**	p = .059	**5p = .039**	**9p = .049**	p = .371
Cond/	F = .656	F = .818	F = 1.013	F = .749	F = 1.287	F = 1.212	F = 1.071	F = 1.357	F = .982	F = 1.165	F = .782	F = .638	F = .783	F = .760	F = 1.292
sens	p = .835	p = .672	p = .454	p = .672	p = .282	p = .327	p = .406	p = .237	p = .477	p = .319	p = .683	p = .882	p = .723	p = .674	p = .282
AD patients															
Deep encoding/old-new effect/raw data															
cond	F = 1.838	F = .063	F = .326	F = 5.795	F = 2.440	F = 1.414	F = 3.336	F = .294	F = .454	F = .284	F = .052	F = .392	F = 1.664	F = .020	F = 1.820
	p = .247	p = .814	p = .599	p = .074	p = .193	p = .300	p = .142	p = .616	p = .537	p = .622	p = .831	p = .565	p = .267	p = .893	p = .270
Cond/	F = .660	F = 1.010	F = .850	F = 1.483	F = 1.089	F = 2.650	F = 1.020	F = .879	F = .803	F = 1.166	F = 1.409	F = 1.620	F = 1.621	F = 2.031	F = 1.314
sens	p = .626	p = .430	p = .510	p = .276	p = .389	p = .467	p = .424	p = .478	p = .494	p = .363	p = .241	p = .194	p = .155	p = .107	p = .316
AD patients															
Shallow encoding/old-new effect/raw data															
cond	F = .786	F = 1.409	F = .054	F = .255	F = .007	F = .745	F = 2.710	F = .069	F = .062	F = .141	F = .005	F = .710	F = .812	F = 1.575	F = .207
	p = .425	p = .301	p = .828	p = .640	p = .936	p = .437	p = .175	p = .806	p = .816	p = .726	p = .946	p = .447	p = .419	p = .278	p = .680
Cond/	F = .895	F = 1.758	F = 1.561	F = 1.354	F = 1.780	F = 1.434	F = 1.282	F = .834	F = .647	F = .637	F = .481	F = .353	F = .460	F = .280	F = .215
sens	p = .515	p = .151	p = .218	p = .263	p = .071	p = .176	p = .271	p = .620	p = .859	p = .869	p = .939	p = .929	p = .882	p = .922	p = .943

rejections (although this difference did not reach statistical significance ($p = 0.118$; $T = -1.986$) there is an obvious trend). On the other hand, the pattern of reaction times after deep encoding obviously differed compared to controls.

Deep encoding: MEG difference maps averaged for both groups separately and for individuals within each group: Correctly recognised repetitions (hits) minus correctly rejected new words (correct rejections)



After deep encoding the mean reaction time related to false alarms did not at all differ from the mean reaction time related to correct rejections ($p = 0.726$; $T = 0.376$). Table 2 provides the values related to every single participant.

3.2 Physiological results

The Repeated Measurement statistical design was applied to raw and normalised data sets of patients and controls in order to calculate condition main effects (*cond*) and condition/sensor location (*cond* ∗ *sens*) interactions. Mean femtoTesla amplitudes of 100 ms intervals were used as dependent variables. Conditions of interest were ''correctly recognised repetitions'' and ''correctly classified new words''. Whereas raw data sets include variations in amplitude normalised data sets include functional aspects.

3.2.1 Raw data

In the deep encoding experiment in controls, a significant *cond* effect occurred for the interval from 250 ms to 350 ms after stimulus onset. Significant *cond* ∗ *sens* interactions occurred for the intervals from about 200 ms–500 ms

Fig. 4. MEG difference maps averaged across all participants within each group (early AD patients and controls) for showing the distribution of significant physiological differences between correctly recognised repeated words (hits) and correctly judged new words (correct rejections) after deep encoding. In principal, an active neural generator produces a magnetic field flux represented by an outcoming field component (positive fT values) and by an ingoing field component (negative fT values). *Upper part:* In controls the areas where significant differences occurred as revealed by paired t-tests for every single sensor location are marked with white circles. In addition, all difference maps are also shown for every single control participant. Note, that every control participant demonstrates a very similar difference magnetic field distribution within the relevant period of time during which significant differences occurred across the whole group of control participants. Furthermore, sensor location maps showing the distribution of significant differences between hits and correct rejections as calculated with paired t-tests for every single sensor location are shown for raw data and for normalised data (Red filled circles represent sensor locations where t-tests revealed significant differences with p-values <.01, orange filled circles represent sensor locations with p-values between .01 and .04 and yellow filled circles represent sensor locations with p-values between .04 and .05). Finally, a single sensor is shown demonstrating differences between fT-values related to hits and correct rejections after deep encoding. *Lower part:* In AD patients the respective average difference map does not allow any such assumption. No statistical significance occurred for the comparison of the magnetic field distributions related to hits and correct rejections. In addition, difference maps are also shown for every single patient. Note, that the difference magnetic field distributions of all AD patients are quite different and do not allow any general statement which results in the lack of any statistically significant effect across the whole group of patients. The sensor location maps showing the distribution of significant differences between hits and correct rejections as calculated with paired t-tests for every single sensor location demonstrate the absence of any significant result (Red filled circles represent sensor locations where t-tests revealed significant differences with p-values <.01, orange filled circles represent sensor locations with p-values between .01 and .04 and yellow filled circles represent sensor locations with p-values between .04 and .05). Finally, the same single sensor, as in controls, is shown demonstrating the absence of differences between fT-values related to hits and correct rejections after deep encoding at a relevant location

Table 3. ANOVA results of normalised data for controls and early AD patients for deep encoding: P-values of cond main effects and *cond * sens* interactions are displayed for consecutive 100 ms time intervals (overlapping for 50 ms). Significant values are bold

Interval	0–100	50–150	100–200	150–250	200–300	250–350	300–400	350–450	400–500	450–550	500–600	550–650	600–700	650–750	700–800
Controls															
Deep encoding/old-new effect/normalised data															
cond	F = .202	F = .122	F = 3.599	F = .031	F = .839	F = 4.873	F = .619	F = .478	F = .034	F = .814	F = .973	F = .072	F = .048	F = .157	F = 1.269
	P = .676	P = .744	P = .131	P = .869	P = .412	P = .092	P = .475	P = .527	P = .864	P = .418	P = .380	P = .802	P = .837	P = .712	P = .323
Cond/	F = 1.308	F = 1.119	F = .996	F = 1.569	F = 1.670	F = 1.453	**F = 1.986**	**F = 3.648**	F = 2.165	F = 1.467	F = 1.696	F = 1.684	F = 1.054	F = 1.041	F = 1.248
sens	P = .203	P = .382	P = .437	P = .199	P = .115	P = .098	**P = .005**	**P = .012**	P = .099	P = .248	P = .168	P = .143	P = .419	P = .420	P = .273
AD patients															
Deep encoding/old-new effect/normalised data															
cond	F = 3.131	F = .465	F = 7.103	F = 2.423	**F = 13.38**	F = 7.221	F = .501	F = .003	F = .557	F = 3.294	F = 1.672	**F = 15.14**	F = 5.399	F = .009	F = .191
	P = .152	P = .533	P = .056	P = .195	**P = .022**	P = .055	P = .518	P = .958	P = .497	P = .144	P = .266	**P = .018**	P = .081	P = .928	P = 691
Cond/	F = .718	F = .751	F = .796	F = 1.481	F = .898	F = .669	F = .788	F = .819	F = .697	F = 1.182	F = 1.257	F = 1.260	F = 1.359	F = 1.897	F = .980
sens	P = .624	P = .671	P = .572	P = .262	P = .497	P = .795	P = .651	P = .575	P = .635	P = .334	P = .276	P = .292	P = .253	P = .071	P = .478

after stimulus onset (Huynh-Feldt corrected) (see Table 2). In patients, neither a significant *cond* effect nor significant *cond* ∗ *sens* interactions were found.

In the shallow encoding experiment in controls significant *cond* effects occurred for the interval from 200 ms to 300 ms and from about 350 ms to 750 ms after stimulus onset (see Table 2). No significant *cond* ∗ *sens* interactions were found. In patients neither significant *cond* effects nor significant *cond* ∗ *sens* interactions occurred.

These results indicate that topographical effects related to the ''old/new'' effect (as represented by significant *cond* ∗ *sens* interactions) only occurred in the control group after deep encoding and are diminished in early AD patients with respect to amplitude differences.

3.2.2 Normalised data

In the deep encoding experiment in controls significant *cond* ∗ *sens* interactions occurred for the intervals from about 300 ms to 450 ms after stimulus onset (see Table 3). In patients *cond* effects occurred for the intervals from 200 ms to 300 ms and from 550 ms to 650 ms after stimulus onset. No significant *cond* ∗ *sens* interactions occurred.

In the shallow encoding experiment in controls a significant *cond* effect occurred for the interval from 600 ms to 700 ms after stimulus onset. In patients a significant *cond* effect occurred for the interval from 200 ms to 300 ms after stimulus onset. In none of the groups did significant *cond* ∗ *sens* interactions occur.

These results indicate that the topographical effects (*cond* ∗ *sens* interactions) related to deep encoding in controls are a matter of functional differences reflecting the engagement of different neural networks related to correctly recognised repetitions and correctly rejected new words.

All together the analysis of the physiological data provide evidence that deep encoding led to physiological differences related to the old/new effect between controls and probable AD patients. Figure 4 shows MEG maps to demonstrate the distribution of difference activities related to the old/new effect in the deep encoding condition for both groups.

4. Discussion

The scientific literature provides a number of reports about neurophysiological differences between AD patients and controls. For example, Dierks et al. (1997) described physiological differences in an EEG study and interpreted their results as reflecting an impaired capability to establish stable brain states necessary for normal brain function in AD patients. In a magnetoencephalographic (MEG) pilot study spectral power and reference-free coherence in 5 patients with early AD were analysed (Berendse et al., 2000). In early AD patients low frequency magnetic power was significantly and rather diffusely increased relative to controls with a fronto-central maximum. On the other hand, high frequency power values were significantly decreased over the occipital and temporal areas. In another MEG study Maestu et al. (2001) found that control subjects showed a higher number of activity sources over the temporal and parietal cortex between 400 and 700 ms after stimulus onset in

a high load probe-letter (targets and distractors) memory task compared to AD patients. In contrast, AD patients showed a higher number of sources over the frontal motor areas, including Broca's area and the insula. Maestu et al. (2001) have been suggesting that a high information load reveals a deficient functioning of phonological store and reduced task-related activity in temporal and parietal areas in AD patients whereas their increased levels of activity in motor areas may reflect a compensatory strategy in an attempt to facilitate rehearsal speed.

Pekkonen et al. (2001) studied with a whole-head magnetometer whether cortical auditory discrimination to duration change as shown by magnetic mismatch negativity (MMNm) response is impaired in AD. They presented a sequence of frequent standard tones embedded with occasional deviants with shorter duration. Their results provide evidence that although MMNm was delayed in the left hemisphere, the automatic discrimination to duration change in the auditory cortex was not attenuated in the early stages of AD. In an earlier MEG study, Pekkonen et al. (1996) also suggested that parallel auditory processing is impaired between the auditory cortices in AD patients.

The present study adds further evidence to distinguish between those two groups both on a psychological and a physiological level. It is firstly important to mention that probable AD patients exhibited a better corrected recognition performance after deep word encoding compared to shallow word encoding as it was the case in the control group. This means that the involvement of conscious semantic information processing during deep word encoding (lexical decision) enhances the chance of subsequent recognition despite the neuropathology related to probable AD (at least at an early stage of the disease). On the other hand, the present behavioural results show that the corrected recognition performances related to both shallow and deep encoding were significantly lower in the patient group as compared to the control group (see Fig. 2). Therefore, these results provide evidence that the reduction in recognition performance in early AD seems to be a general effect which does not differentiate between shallow and deep encoding.

In the introduction the idea was mentioned that the recognition performance might be selectively impaired thinking of deep encoding to be more affected than shallow encoding. Since this is not the case, the present finding supports the idea of an unspecific memory function which seems to be impaired in probable AD patients. This idea might be important due to the notion that different encoding instructions lead to different involvements of neural networks (e.g. Tulving, 1987; Walla et al., 2001). It is therefore important to note that there might exist a general retrieving function equally related to different memory systems. Alternatively, the equal performance reduction for both levels of processing could also be attributed to the encoding phase. Such an idea would be supported by a study by Kato et al. (2001) who demonstrated that mild AD patients showed brain activity only in the visual association areas during the encoding of visual information whereas nondemented controls uniformly showed additional activation in the entorhinal cortex and several other functionally related regions.

In principal, a reduced performance related to probable AD is not surprising. This is at least partly due to the early neuropathology at medial temporal lobe (MTL) areas which are known to be strongly involved especially in explicit memory processes. For example, immediate and delayed recall (especially delayed recall) were even found to be directly related to hippocampal head size in healthy human subjects. Larger hippocampal heads were associated with higher scores in the memory test (Hackert, 2002). Furthermore, reduction of MTL activity in AD patients compared to controls was found during a learning task that required the encoding of new information (objects) into memory using fMRI (Rombouts et al., 2000). Also, fear conditioning, an amygdala-dependent (MTL) form of memory was found to be impaired in AD patients (Hamann et al., 2002).

Shallow encoding like it was performed in the present study is likely to depend more on familiarity based recognition processes (reflecting robust implicit memory functions) than explicit memory functions. As mentioned above, it would therefore be expected that selective impairments do occur in probable AD patients, mainly related to deep encoding which includes explicit processes. At least, this was not the case with respect to recognition performance. On the other hand, the analysis of reaction times related to correctly and incorrectly classified repeated and new words revealed strong evidence of the idea that brain functions related to deep verbal information processing are specifically affected in probable AD patients. As demonstrated in Fig. 3 it was obviously the deep encoding condition which led to a different pattern of reaction times. The fact that reaction times related to the condition of false alarms (new words wrongly classified as repeated) seems to be affected in particular could be of principal interest for memory research. For the present investigation this specific effect is difficult to interpret because the phenomenon of false recognition which is reflecting the fact that some of the new items in a recognition test are falsely classified as repeated is not fully understood. Further work has to be done in order to augment the understanding of this phenomenon and its possible role for an early diagnosis of the AD. However, in a recently published study (Püregger et al., 2003) about levels of processing in mild cognitive impairment (MCI) patients the analysis of reaction times revealed very similar results. In that study, recognition performance did not differ between MCI patients and controls whereas within both groups deep encoding led to an enhanced recognition performance compared to shallow encoding. Although not at all impaired with respect to recognition performance MCI patients demonstrated psychomotor deficits as reflected by modulated reaction times similar to the probable AD patients of the present study. This comparison is interesting because 10%–15% of MCI patients per year do develop the AD (Petersen et al., 2001). Certainly, any contribution to an early diagnosis is highly appreciable. The fact that a simple parameter like a reaction time value within a word recognition experiment could represent a reliable tool for an early diagnosis of the AD is promising.

Gainotti et al. (2001) suggested that psychomotor speed and lower levels of attention are preferentially impaired in subcortical forms of dementia such as multi-infarct dementia, whereas higher levels of selective and divided attention

are more markedly disrupted in the Alzheimer type of dementia. Indeed, in our study psychomotor speed was not affected in principal related to probable AD patients. Strikingly, reaction times related to distinct cognitive processes were affected.

Finally, the analysis of the physiological data most obviously demonstrate that differences between probable AD patients and controls might rather be linked to deep encoding and therefore reflect rather conscious memory deficits. In controls, correctly recognised repeated words (hits) produced higher femto-Tesla values than correctly rejected new words (correct rejections) (old/new effect) mainly over posterior brain areas after deep encoding. This effect was topographically significant between about 300 ms and 450 ms after stimulus onset with respect to functional aspects (as revealed by the analysis of normalised data). This effect was missing in probable AD patients. The old/new effect, as it is described in memory research, is thought to reflect neurophysiological processes which either contribute to or are contingent upon conscious memory (see Allan et al., 1997). For this reason, the lack of such an effect in early AD patients can be interpreted as reflecting an impairment in conscious memory retrieval. Although the exact location of neural substrates being associated with the old/new effect which we found in controls was not determined the distributions of the difference magnetic fields (hits minus correct rejections) allow the assumption that any involved neural structures are located in posterior parts of the brain similar to previous ERP findings (e.g. Rugg, 1995). Those areas are often linked to associative functions. As mentioned in the introduction, neuropathology of the AD spreads from medio-temporal brain structures at early stages to association areas at later stages of the disease (e.g. Braak and Braak, 1995). This means that at early stages posterior brain areas are not yet affected and should be normally functioning. The lack of an old/new effect as it was found in the present study can therefore rather be related to dysfunctions in the medio-temporal area.

Differences between AD patients and controls depending on depth of verbal encoding were also found in another study. Beauregard et al. (2001) found that after shallow and deep encoding of study words word stem completion (WSC) overall priming was equivalent in AD patients and controls. Only after deep encoding (semantic processing) the priming effect noted in AD patients was significantly smaller for semantically degraded items than for semantically intact items. The authors suggested that the degree of semantic impairment represents one important variable affecting the amount of WSC priming.

However, our results demonstrate evidence of a selective psychomotor impairment and an altered neurophysiology related to deep word processing. This finding is strongly supported by previous studies reporting about a semantic memory loss related to the AD (Nebes, 1989; Chertkow and Hub, 1990; Giffard et al., 2001, 2002) because our deep encoding instruction was to make a lexical decision (animate/inanimate discrimination) representing semantic information processing.

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