A cognitive perspective on clinical manifestations of Alzheimer s disease

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EEG abnormalities are associated with different cognitive profiles in Alzheimer's disease

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Abstract

Objective: To investigate associations between different cognitive profiles and their underlying functional brain changes as measured by electroencephalogram (EEG) in Alzheimer's disease (AD).

Methods: EEG was obtained and neuropsychological performance assessed in 254 patients with AD. EEG's were visually assessed for the presence of focal and/or diffuse abnormalities. Multivariate analysis of variance (MANOVA) for repeated measures was performed with presence of focal and/or diffuse abnormalities as between-subjects factors, and neuropsychological tests as within-subject factor. Age, sex and education were entered as covariates.

Results: 28% of patients had a normal EEG, 32% had focal abnormalities, 14% diffuse abnormalities and 26% had both focal and diffuse abnormalities. Patients with a normal EEG presented with a cognitive profile, in which memory was mostly impaired. Patients with focal and diffuse EEG abnormalities presented with a non-memory profile.

Conclusion: These results illustrate that specific types of EEG abnormalities are associated with different cognitive profiles in AD, providing biological support in terms of brain functioning for variability in cognitive impairment.

Introduction

Alzheimer's disease (AD) is the most common form of dementia. Typically, memory deterioration anticipates impairment of other cognitive domains [1]. However, individual patients may show relative sparing of memory and more prominent impairment of visuo-spatial skills, executive skills, praxis or language [2]. It seems that patients with AD may present with different cognitive profiles. More specifically, it has been suggested that in addition to the typical memory phenotype patients may also present with a non-memory phenotype [3-5]. The question remains, if this heterogeneity in cognitive presentation has a biological basis in terms of brain functioning.

Electroencephalogram (EEG) records the electrical activity of cortical neurons and thus provides a direct measure of brain function. In general, the EEG in AD is characterized by diffuse slowing [6-8]. Focal abnormalities are associated with Vascular Dementia (VaD), but are not uncommon in AD [6-10]. The sensitivity of visual EEG analyses in differentiating AD from healthy controls or other dementias varies in different studies from 0.45 -0.88 [7]. These numbers underscore that EEG can also be normal in patients with AD [11-13].

There are only a few studies assessing the relationship between EEG abnormalities and cognitive impairment in AD, mostly limited to the Mini-Mental State Examination (MMSE). These studies concluded that severity of EEG abnormalities was associated with severity of cognitive impairment [13-16]. A few, only small, studies examined relations with impairment in specific cognitive domains. One small study reported an association between decreased alpha reactivity and more severe impairment of memory and executive functioning [17]. Another preliminary study concluded that patients with slow-wave activity in their EEG had a distinct pattern of cognitive decline in which language, visual functions, retrieval from semantic memory and praxis were more impaired [18]. These preliminary studies suggest that changes in brain activity as reflected by the EEG are not only related to the severity of cognitive impairment, but also to the cognitive phenotype.

In this study, we investigated the association between different cognitive profiles and their underlying functional brain changes as measured using EEG in AD. We included a large cohort of patients with AD who were grouped by presence and type of abnormalities in their EEG and assessed relations with performance in a number of cognitive domains.

Methods

Subjects

Consecutive patients (n=378) with AD were recruited from the outpatient memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc). They all underwent a standardized one-day assessment including medical history, informant-based history, physical and neurological exam, laboratory tests, neuropsychological assessment, EEG and magnetic resonance imaging of the brain. Diagnoses of probable AD were made in a multidisciplinary consensus meeting [1]. Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated) [19].

Use of psycho-active drugs was recorded. The following drugs were considered to be psychoactive: benzodiazepines (n=21), anti-depressants (n=17), anti-psychotics (n=3), anti-epileptic drugs (none), methylphenidate (n=1) and acetylcholinesterase inhibitors (n=13), memantine (none) or a combination of the above (n=9). These patients (n=64) were excluded from analysis. Twenty-nine patients with a medical history, which could influence EEG, were excluded from further analysis (previous severe head trauma (n=8), epilepsy (n=5), stroke (n=11), alcohol abuse (n=2), multiple sclerosis (n=1), neurolues (n=1), oncology (n=1)).

Furthermore, 31 patients with an incomplete neuropsychological assessment were excluded from analysis. This resulted in a study sample of n=254 patients with AD. The study was approved by the local Medical Ethics Committee. All patients gave written informed consent for their clinical data to be used for research purposes.

Neuropsychological assessment

Cognitive functions were assessed by a short, standardized test battery. To assess dementia severity the MMSE was used [20]. For attention we used the extended version of Digit Span forward condition and we used the backward condition of this test for working memory [21]. In the forward condition, patients are asked to repeat sequences of digits. In the backward condition patients are asked to repeat sequences of digits in reverse order. Each sequence of digits consists of three trials. Both conditions start with a two-digit sequence and may end with an eight-digit sequence. Scores can vary between zero and 21. The Visual Association Test (VAT) was used to assess memory [22]. The VAT consists of six cue images and the same six images with an interacting image on twelve separate cards. The patient is asked to name the images. Without delay the six cue image cards are shown and the patient has to recall the missing interacting object. If the patient does not recall all interacting objects, the procedure is repeated for a second trial. The scores of the first and second trial are summed to obtain a total score varying between 0 and 12. The Visual Association Test object naming was used to assess language (0-12). To evaluate executive function and language we used category Fluency. In this test patients have to name as many animals as possible within a time limit of one minute. To assess mental speed we administered Trail Making Test (TMT) A in which the patient has to connect digit 1 to 25 as quickly as possible by pencil [23]. To evaluate executive functioning we used the more complex TMT B in which the patient has to alternate between digits and numbers (e.g. 1-A-2-B-3-C etc.). In both tests time required for completion was recorded.

EEG Protocol

Twenty-one channel EEGs were recorded during 30 minutes, using the Nihon Kohden digital EEG apparatus (EEG 2100), and since September 2003, OSG digital equipment (Brainlab®) at the positions of the 10-20 system: Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz, Pz. Sample frequency was 200 Hz for the Nihon Kohden system and 500 Hz for the OSG Brainlab system. Electrode impedance was less than 5kΩ. Initial filter settings were: time constant, 1 sec; low pass filter. 70 Hz. Patients sat in a slightly reclined chair, predominantly with eyes closed, and they were kept awake as much as possible during the recording.

Visual EEG assessment

All EEG recordings were interpreted visually by one of three experienced, board-certified, clinical neurophysiologists without knowledge of clinical information. Part of the routine judgment included assessment of presence of focal and/or diffuse EEG abnormalities.[9] Focal abnormalities were defined as (transients of) slow or sharp wave activity in one or more EEG leads, excluding benign temporal theta of the elderly (BTTE) [12]. For diffuse abnormalities, dominant frequency of rhythmic background activity below 8 Hz, diffuse slow-wave activity and diminished reactivity of the rhythmic background activity to the opening of the eyes were each considered as a criterion. In this study, both were considered as dichotomous variables. We have previously shown interobserver agreement to be moderate for focal abnormalities (kappa 0.60) and good for diffuse slowing (kappa 0.87) [9].

Statistical analysis

SPSS 15.0 for Windows was used. TMT A and B scores were log-transformed because they were not normally distributed. To allow comparison of test performance on the various tests between and within patients, multivariate analysis of variance (MANOVA) for repeated measures was performed with focal and diffuse abnormalities as between-subjects factors, and above mentioned seven neuropsychological tests as within-subject factor. Age, sex and education were entered as covariates. In this model, the neuropsychological tests are considered the repeated measurements. All neuropsychological data were standardized into z-scores, to allow comparison of results on different neuropsychological tests within patients. TMT A and B scores were inverted by computing -1*z-score, because higher scores imply a worse performance. The significance level was set at $p < 0.05$.

Results

Age (mean±SD) was 72±9 years and 124 patients (49%) were female. On average all patients were mildly to moderately demented (MMSE 22±4). Among the 257 patients with AD, 72 (28%) had a normal EEG, 82 (32%) had only focal abnormalities, 34 (14%) had only diffuse abnormalities and 66 (26%) had both focal and diffuse disturbances, as can be seen in table 1. No age differences were found between patients with focal abnormalities (71±9) and patients without focal abnormalities (73± 8;p=.08) or between patients with diffuse abnormalities (71±10) and patients without diffuse abnormalities (72±8;p=.32). In patients with focal abnormalities there were more women (55%) than among patients without focal abnormalities (41%;p=.03). In patients with diffuse abnormalities there were less women (36%) than among patients without diffuse abnormalities (57%;p=.001). Regarding MMSE-scores, there were no differences between patients with focal abnormalities (21±4) versus patients without focal abnormalities (22±5;p=.20), or between patients with diffuse abnormalities (21±5) versus patients without diffuse abnormalities (22±4;p=.23).

MANOVA for repeated measures was performed to assess the effects of diffuse and focal EEG abnormalities on neuropsychological functioning. We found a main effect for diffuse abnormalities on neuropsychological performance ($F(1,247)= 22.1$; $p<.001$), but not for focal abnormalities ($F(1,247)=1.9$; $p=.17$). There was an interaction between focal and diffuse disturbances ($F(1,247)=5.2$; $p=.02$). Furthermore, there was an interaction between focal abnormalities and neuropsychological performance ($F(6,242)=2.7$; $p=.01$). There was no interaction between diffuse abnormalities and neuropsychological testing ($F(6,242)=1.6$; $p=.16$). There was no two way interaction between focal and diffuse abnormalities and neuropsychological testing ($F(6,242)=1.03$; $p=.41$).

Figure 1 shows test performances according to the presence of focal and/or diffuse EEG abnormalities. As can be appreciated in the figure, the groups of patients show different cognitive profiles. Overall, patients with no abnormalities in their EEG showed best performance on neuropsychological testing compared to the other groups, with most prominent impairment on the VAT. Performance of patients with isolated focal abnormalities was intermediate, with performance on all tests around the overall group average. These patients performed relatively worse on category Fluency and TMT B. Patients with only diffuse abnormalities in general performed less on neuropsychological testing compared to the other groups. Their performance was most impaired on TMT A, TMT B, VAT and Digit Span backward. Patients with both diffuse and focal abnormalities showed a distinct cognitive profile with relative sparing of performance on the VAT and most prominent impairment on other tasks, including Digit Span forward and backward, and TMT A and B.

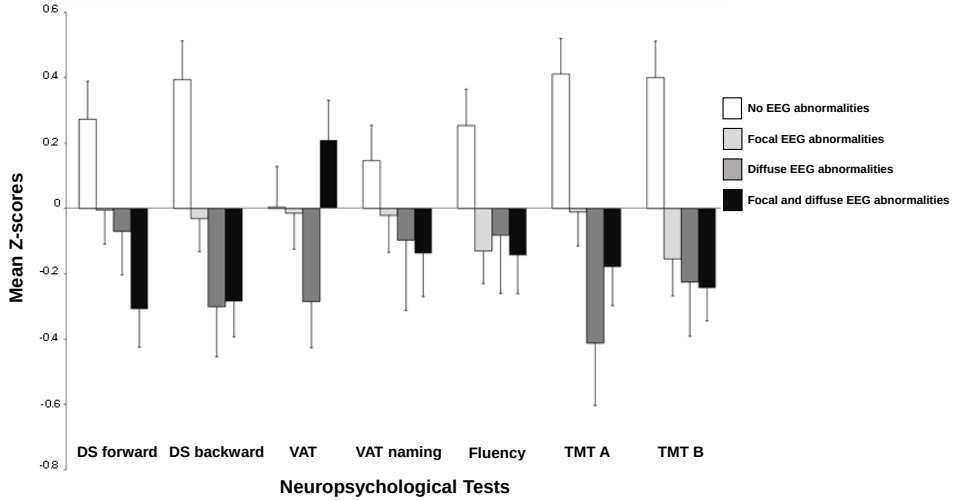
Table 1. Demographics and neuropsychological test performance of patients according to EEG abnormalities.

Type of EEG abnormalities	Normal	Focal	Diffuse	Focal and Diffuse
Number of patients, N	72	82	34	66
Number of women, N (%)	35 (49)	53 (65)	8 (24)	28 (42)
Age in years	73 ± 7	72 ± 8	73 ± 10	70 ± 9
Level of education [#]	5 ± 1	5 ± 1	5 ± 1	5 ± 1
Mini-Mental State Examination	23 ± 4	21 ± 4	21 ± 5	21 ± 5
Digit Span, forward condition	12 ± 3	11 ± 3	11 ± 2	10 ± 3
Digit Span, backward condition	8 ± 3	7 ± 2	6 ± 2	6 ± 2
Visual Association Test, memory	5 ± 4	5 ± 4	4 ± 3	5 ± 4
Visual Association Test, naming	11 ± 1	11 ± 1	11 ± 1	11 ± 1
Category Fluency	14 ± 5	12 ± 4	12 ± 5	12 ± 5
Trail Making Test A (in seconds)*	78 ± 67	99 ± 72	129 ± 89	111 ± 91
Trail Making Test B (in seconds)*	276 ± 141	375 ± 154	387 ± 160	379 ± 141

Age and performance on neuropsychological testing presented as mean±standard deviation.

[#] according to the Verhage-system, * higher scores implies worse performance.

Figure 1. Mean neuropsychological Z-scores by EEG abnormalities.



The x-axis shows the individual neuropsychological tests; the y-axis shows the mean z-scores (and standard errors) corrected for sex, age and education. Z-scores allow comparison of neuropsychological tests results within patients. DS: Digit Span; VAT: Visual Association Test; TMT: Trail Making Test. Z-scores of TMT were inverted; as a result higher z-scores imply better performance on all tests.

Discussion

We showed that presence and type of EEG abnormalities are not only associated with dementia severity, but also with the profile of cognitive impairment. Among AD patients with a normal EEG, poorest performance was observed on the memory task. They show a cognitive profile in which memory was most impaired. Patients with both focal and diffuse abnormalities show an atypical cognitive profile in which cognitive domains other than memory are most impaired. These results provide evidence that different cognitive profiles in AD are related to specific underlying changes in brain activity, as reflected by EEG abnormalities.

In our study a substantial proportion (28%) of patients with AD showed no EEG abnormalities, in accordance with previous studies [9,11-13,24]. Neuropsychological test scores were relatively least impaired in this group of patients. Differences were small however, as despite their normal EEG, all patients were mildly to moderately demented as measured with the MMSE (23±4). These patients with a normal EEG showed a typical Alzheimer cognitive profile, with relatively poorest performance on memory.

Patients with only diffuse abnormalities were in general most severely impaired on neuropsychological testing and slightly more impaired on global cognition (MMSE 21±5), in line with former studies [13,15,16]. The present study extends these findings, as we took into account performance on specific neuropsychological tests. The cognitive profile of patients with only diffuse abnormalities was most impaired on mental speed, executive functioning, memory and working memory, while language was relatively preserved.

Patients with isolated focal abnormalities performed around the overall group average for all tests. These patients performed relatively worse on executive tasks and relatively better at tests appealing attention, mental speed and memory. Focal abnormalities have been associated with VaD and have been found in patients with AD with a vascular component [6-10]. In our study, however, mental speed – which is commonly considered to be characteristic of vascular damage – was most impaired in patients with only diffuse abnormalities, rather than in patients with only focal abnormalities. Given the association between focal abnormalities and vascular pathology, future research to explore a possible relationship between focal EEG abnormalities and the localisation of vascular pathology on MRI could be of interest.

Finally, patients with both focal and diffuse abnormalities showed a distinct cognitive profile with performance mostly impaired on attention, working memory, executive functioning and mental speed. Typically, memory performance was relatively preserved in these patients. It seems that presence of both focal and diffuse abnormalities is related to a non-memory phenotype in AD. In our sample the group of patients with focal and diffuse abnormalities were younger than the other groups of patients. This is in line with studies who found more EEG abnormalities in younger patients [25,26].

Earlier studies have shown that there may be a genetic basis of this non-memory phenotype, as it was more commonly observed in apolipoprotein (APOE) Ɛ4-negative patients with AD [3,4,27]. By contrast, APOE Ɛ4-positive patients mostly showed a typical memory phenotype. On MRI, medial temporal lobe atrophy is typically found in AD, and has been related to impaired memory [28]. A number of patients however present with posterior, rather than medial temporal lobe atrophy, and it has been suggested that these patients have an atypical AD presentation and show more rapid decline over time [29-32].

Earlier studies concluded that APOE genotype may have a regional influence on atrophy pattern in AD. In APOE Ɛ4-positive patients increased atrophy is observed in the (medial) temporal lobes, whilst in APOE Ɛ4-negative patients increased atrophy is observed in the frontal and/or posterior areas [33-35]. A recent study showed that APOE Ɛ4-negative patients have more prominent focal and diffuse EEG abnormalities than APOE Ɛ4-positive patients [26]. It is tempting to think that patients with both focal and diffuse abnormalities, presenting with a non-memory phenotype, are younger, more often APOE Ɛ4-negative and have more prominent posterior and/ or frontal atrophy. In the current study, we found evidence for more prominent changes in brain activity in patients presenting with a non-memory phenotype. Future research should attempt to relate these functional changes to structural brain changes.

Among the strengths of this study is the large cohort of patients with AD, who were all examined standardized procedure including EEG and cognitive testing. By using a neuropsychological test battery, we took a close look at specific cognitive functions instead of being limited to global cognitive decline. A potential limitation is the absence of tests assessing visuo-spatial functions and praxis. Furthermore, we used dichotomous EEG ratings, which might be not sensitive enough to notice subtle EEG changes. However, since healthy elderly may have subtle EEG changes as well, we feel confident that our simple EEG rating scheme is sensitive enough to detect clinical relevant changes [19].

In conclusion, specific types of EEG abnormalities are associated with different cognitive profiles in AD, showing that there is biological support in terms of brain functioning for variability in cognitive profile in AD.

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