Original Research Article

Quantitative EEG Applying the Statistical Recognition Pattern Method: A Useful Tool in Dementia Diagnostic Workup

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Key Words

Dementia · Alzheimer's disease · Lewy body dementia · Quantitative EEG · Diagnostic assessment · Validity

Abstract

Background/Aim: The aim of this study was to examine the discriminatory power of quantitative EEG (qEEG) applying the statistical pattern recognition (SPR) method to separate Alzheimer's disease (AD) patients from elderly individuals without dementia and from other dementia patients. **Methods:** The participants were recruited from 6 Nordic memory clinics: 372 unselected patients [mean age 71.7 years (SD 8.6), 54% women] and 146 healthy elderly individuals [mean age 66.5 years (SD 7.7), 60% women]. After a standardized and comprehensive assessment, clinical diagnoses were made according to internationally accepted criteria by at least 2 clinicians. EEGs were recorded in a standardized way and analyzed independently of the clinical diagnoses, using the SPR method. **Results:** In receiver operating characteristic curve analyses, the qEEGs separated AD patients from healthy elderly individuals with an area under the curve (AUC) of 0.90, representing a sensitivity of 84% and a specificity of 81%. The qEEGs further separated patients with Lewy body dementia or Parkinson's disease dementia from AD patients with an AUC of 0.9, a sensitivity of 85% and a specificity of 87%. **Conclusion:** qEEG using the SPR method could be a useful tool in dementia diagnostic workup.

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Introduction

Dementia is one of the major health challenges worldwide. Due to a large increase in older individuals, the number of people suffering from dementia will grow from about 35 million today to more than 100 million during the next 30 years [1, 2]. Several brain disorders can cause dementia, but in more than half of the cases, Alzheimer's disease (AD) is the primary underlying condition, followed by dementia caused by stroke, Lewy body dementia (LBD) and several other forms of neurodegenerative disorders of the frontal or temporal lobes (or a combination of both) in the brain. Although no cure exists for any of the degenerative brain disorders causing dementia today, it is of great importance to make a correct diagnosis in patients with symptoms that may indicate dementia as soon as possible. First and foremost, several studies have indicated that up to half of the patients referred for dementia evaluation do not have dementia but may suffer from other, potentially reversible conditions – depression being the most frequently encountered [3]. Moreover, symptomatic drug treatment exists for AD, LBD and Parkinson's disease dementia (PDD) and should be offered to patients together with proper care planning, including support to both patients and family caregivers throughout the progression of the disease.

To diagnose a dementia disorder, clinical criteria are applied based on findings from comprehensive clinical assessments. However, most of these clinical criteria are not very helpful when patients seek health care services in a very early phase of a dementia disorder [4]. Thus, there is a need for sensitive and precise diagnostic tools that can detect brain disorders that will eventually lead to dementia. New specific research criteria for AD have been proposed, in which biomarkers have a central role [5–8]. The use of various MRI techniques, PET and SPECT methods as well as examination of spinal fluid measuring the concentrations of β -amyloid and phosphorylated and total tau protein have been shown to be helpful in diagnosing AD and to separate AD from other brain disorders causing dementia [5, 9–12]. However, these methods have mainly been used at academic centers. Some of these diagnostic tools are very expensive (PET), some are invasive (tapping of spinal fluid), and some methods need personnel with high expertise to evaluate the findings (MRI). For these reasons, some of the above-mentioned biomarkers cannot be applied in countries with a poor economy, and some will not be applied in countries where doctors are reluctant to use invasive methods. Thus, there is a need for diagnostic biomarkers that can be applied more widely than PET, MRI and spinal fluid markers.

EEG has the potential for being such a biomarker, as it is cheap, noninvasive and simple to use and can be applied outside academic centers. The main EEG abnormalities in AD are slowing of alpha activity and increases in theta and delta activities, and these changes correspond well with the severity of AD [13–15]. Quantitative data from EEG recordings are generated by use of computerized analysis [16], and quantitative EEG (qEEG) parameters have repeatedly shown good discriminatory power between different dementia disorders and healthy aging in a number of clinical studies [17–21]. However, no evidence exists that supports a single, most accurate qEEG discriminator for different dementia syndromes and disease severity. There is also no agreement on the best classification algorithm based on qEEG parameters to be used in a routine diagnostic process for individual patients [18].

A new way to analyze EEG recordings is being developed in Iceland by MentisCura [22]. This method is based on a mathematical model, the statistical pattern recognition (SPR) method. It is an advanced model that aims to recognize and classify new data from EEG recordings based on comparison with normative data from well-defined patients with various dementia disorders and from healthy controls. An Icelandic databank used for the SPR method contains EEG recordings from more than 1,000 patients with various dementia diagnoses and from about 500 healthy controls. The Icelandic database has been used in order to develop

various classifiers contrasting different sub-cohorts. These classifiers can then be applied to subsequent EEG recordings, constituting an independent estimate of the properties of the classifiers. Only few studies have been published that aimed to validate the SPR method. The first pilot study that included a small number of AD patients with dementia of moderate degree and normal controls showed that the method had good sensitivity and specificity to separate AD patients from healthy controls [23]. A second Norwegian study, including about 100 unselected patients referred to a memory clinic, could not replicate the findings from the Icelandic pilot study [24]. However, a later study from Iceland that included a large group of patients referred to a memory clinic and normal controls showed very promising results both in separating AD patients from normal controls and in separating AD patients from patients with other forms of dementia and from those with mild cognitive impairment (MCI) [25]. Thus, conflicting results were reported in different studies that included patients from two different memory clinics.

The aim of the present study was to examine the discriminatory power of qEEG to separate patients with AD in a very early phase of the disease from elderly persons without dementia, using the SPR method. Subsequently, we wanted to examine if the SPR method could be used to differentiate common types of dementia disorder from each other.

Subjects and Methods

Participants

The study was conducted by including patients and healthy elderly controls from 6 Nordic memory clinics which are members of the Nordic Network in Dementia Diagnostics (NIDD). These memory clinics are located at the University Hospitals in Copenhagen and Roskilde (Denmark), at the Deaconess Hospital in Bergen and the Oslo University Hospital (Norway), at Karolinska Institutet in Stockholm (Sweden) and at the Landspítali National University Hospital in Reykjavik (Iceland). In order to ensure that about 20 patients were in each diagnostic group (which is a common requirement for validation studies), each center needed to include a minimum of 60 patients and 20 controls. Patients coming for their first assessment were recruited randomly, and in most of the clinics, they were included consecutively. However, this was not possible in all cases, as only 1 physician per clinic took part in the study. We do not have an overview of how many patients declined participation.

The selection was performed according to the following predefined exclusion criteria: significant neurological disorder with dementia other than AD, PDD and LBD, major psychiatric disorders and alcohol or drug abuse. In all, we included 377 patients. Due to poor quality of the EEG recording, 5 patients were excluded, leaving 372 patients for the analyses. The 5 excluded patients did not differ from the included patients with regard to any characteristics as shown in table 1. The controls were 146 elderly persons; they were recruited from among family members of the patients, were employees at the 6 hospitals that participated in the study or were recruited by advertising.

Clinical Diagnostic Assessment

All patients were examined according to the standard at each memory clinic, which was similar at all 6 clinics. Clinical assessment consisted of the following: a history from the patient and an informant, a physical examination with the focus on neurological and cardiologic status, blood tests to screen for disorders that could be associated with cognitive impairment, neuropsychological tests covering various cognitive domains as well as CT or MRI of the brain for the evaluation of white matter changes, general atrophy and atrophy of the medial temporal lobes. Lumbar puncture was done for examination of β -amyloid and total tau and phosphorylated tau protein in the cerebrospinal fluid when indicated (about half of the patients). Some patients were assessed with PET or SPECT. Details of the comprehensive assessment, which was similar in all 6 memory clinics, can be found in a previously published paper [26].

The clinical diagnoses were made at consensus meetings with all doctors present at the memory clinic, or by at least 2 experienced doctors, and they applied the DSM-IV-R and the McKhann criteria for the diagnosis of AD, the NINDS-AIREN criteria for vascular dementia, the revised consensus criteria for LBD and the Lund-Manchester criteria for frontotemporal dementia [27–30]. Unspecified dementia and dementia due to

Table 1. Features that were used to create the healthy control index, the AD index and the DLB/PDD index

Control vs. clinical		AD vs. clinical		DLB/PDD vs. clinical	
coherence	feature	coherence	feature	coherence	feature
Fp2/P4	TP	Fp1/P3	γ	Fp1/O1	$\beta 1$
C4/O2	θ	F3/O1	$\alpha 2$	Fp2/O2	δ
F7/F8	TP	F4/O2	δ	Fp1/P3	PAF
T3/T4	γ	F4/O2	θ	Fp2/P4	$\beta 2$
T3/T4	PAF	F3/P3	θ	F3/O1	$\alpha 2$
T5/T6	$\alpha 1$	F4/P4	δ	F3/F4	PAF
P3/P4	$\beta 1$	C3/O1	θ	T5/T6	$\alpha 1$
O1/O2	TP	C3/O1	TP	O1/O2	θ
Fp1/F7	$\alpha 2$	C3/O1	PAF	Fp1/F3	θ
Fp2/F8	$\alpha 1$	F7/F8	PAF	Fp1/F3	TP
Fp2/F8	γ	T5/T6	$\alpha 2$	Fp2/F4	TP
Fp2/F8	TP	Fp1/F7	PAF	F7/C3	$\beta 1$
Fp1/F3	$\beta 1$	Fp2/F8	PAF	F3/C3	PAF
F8/C4	θ	Fp1/F3	θ	F4/C4	PAF
F3/C3	PAF	Fp1/F3	PAF	P3/O1	δ
P3/O1	δ	F7/T3	$\beta 2$	C3/T5	θ
P4/O2	γ	T6/O2	θ	C3/T5	γ
C4/T6	$\alpha 1$	C4/T6	$\alpha 1$	C4/T6	$\alpha 1$
C4/T6	TP	P3/C3	θ	P3/C3	$\beta 2$
P4/C4	δ	P4/T6	$\alpha 1$	P4/T6	$\alpha 1$

PAF = Peak alpha frequency; TP = total power.

PDD as well as depression (major depression was excluded) were diagnosed with the ICD-10 criteria for research. The diagnosis of MCI was made using the Winblad criteria, and we subdivided the MCI group into amnesic and nonamnesic MCI subgroups [31]. Patients who did not meet any of the above criteria and had normal cognitive test results according to their age were categorized as having subjective cognitive impairment (SCI). All diagnoses were made independently of the EEG results ('blinded').

The healthy control persons were interviewed, and histories of previous and present disorders and use of drugs were recorded. They were tested with a cognitive test battery (see below) to make sure that they had no cognitive impairment. Any individuals with a test result on a cognitive test below 1 SD according to their age were excluded. Further examinations were not conducted.

Additional Information Used in the Analyses

For the patients, the results of the following cognitive tests were used: (1) the Mini-Mental State Examination (MMSE) [32, 33] (a measure of overall cognitive function consisting of 20 items with a minimum score of 0 and a maximum score of 30, with lower scores indicating more severe cognitive impairment); (2) the Clock-Drawing Test (CDT) [34] (a short screening test of cognition and possibly of visuospatial function; we used the scoring procedure of Shulman, with a minimum score of 0 and a maximum score of 5, with lower scores indicating poorer function), and (3) the 10-word tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [35], which tested the capacity to learn 10 words with 3 repetitions (CERAD-learning; max. score 30), to recall the 10 words after 10 min (CERAD-recall; max. score 10) and to recognize the 10 words among another 10 words (CERAD-recognition; max. score 20). A lower score on each of the 3 tests indicates poorer cognition. Depression was assessed using a modified version of the Montgomery-Åsberg Depression Rating Scale (MADRS) [36]. Each of the 10 items was assessed as present or not, yielding a minimum score of 0 and a maximum score of 10. A higher score denotes more depressive symptoms.

The controls were tested with the MMSE, CDT and CERAD 10-word tests (all 3 parts), and depression was rated with the modified MADRS in the same way as were the patients. Demographic variables such as age, gender, marital status and years of schooling as well as use of drugs and comorbidities were recorded for both the patients and the controls.

EEG Recordings and Evaluation

EEGs were recorded using NicoletOne EEG Systems (Natus®). Subsequent analysis was done in the MATLAB environment (MathWorks®). The IS 10-20 system was used for electrode placement (with 19 electrodes), and the features were evaluated using the average montage. Two bipolar electro-oculography channels and 1 electrocardiogram were applied to monitor artifacts. The EEGs were recorded for at least 3 min, with the subjects at rest with their eyes closed. They were alerted if they became visibly drowsy, since drowsiness influences recording.

qEEG Feature Extraction

For each EEG channel, 20 spectral features were extracted; coherence was estimated for 37 chosen channel pairs, and the same spectral features were extracted as for each individual channel. Thus, a total of 1,120 features were extracted from each EEG recording. The reliability of the EEG features used in this study has already been investigated and described [22].

qEEG Resampling

The EEGs gathered in the present study were sampled at 1,024, 1,000, 512, 500, 256, 250 or 200 Hz in the 6 partaking centers. All EEGs in this study were resampled to 256 Hz in order to make them comparable. In cases where the original sampling was higher than 256 Hz, the samples were downsampled by averaging. If the sampling frequency was 200 Hz, the samples were upsampled by linear bridging between all adjacent points and then sampled at 256 Hz.

qEEG Classifiers

The data are analyzed applying the SPR technique, which is used to construct a classifier from two diagnostic groups of qEEGs, for example, qEEGs from a group A and a group B [23, 25]. When an EEG is classified, the classifier returns an index, the A-B index, with a value between 0 and 1. If the A-B index is close to 0, the EEG is indistinguishable from the EEGs in group A, and if the A-B index is close to 1, the EEG is indistinguishable from the EEGs in group B. In order to minimize the risk of overfitting, each classifier is restricted to rely only on a set of 20 qEEG features out of the 1,120 features available. For each classifier construction there are thus 3×10^{42} distinct possibilities. Hence, a genetic algorithm was applied to select the features used in the construction of the classifier for each pair of groups [37]. The target value for the genetic evolution of classifiers was the area under the curve (AUC) of the corresponding receiver operating characteristic (ROC) curve. The objective was not to find the best classifier in each case – which is a near impossible task – but rather to find a classifier with clinically acceptable qualities.

Three classifiers derived from the data gathered in a previous study [25] were used in the analysis of the qEEG data of the present study. The first one, the 'healthy control index', was constructed to separate a qEEG derived from a healthy individual from that derived from an individual who suffers from MCI or any dementia disorders. The second one, the 'Alzheimer's disease index' (AD index), was constructed to detect AD patients and separate them from the clinical cohort with any diagnosis except AD (not controls). The third one, the 'diffuse Lewy body/Parkinson's disease index' (DLB/PDD index), was constructed to detect patients with LBD or PDD among the clinical cohort and separate them from all other patients in the study (not controls). Each of the recordings gathered in this study was classified by the three indices described above. The classification in our study is comparable with the previous classification used in qEEG studies conducted in Iceland and Norway, which employed the same SPR algorithm. The features used in each of the three indices in the present study are shown in table 1.

Statistics

All data were analyzed using the SPSS software version 20. Continuous data are presented as means and SD. Categorical data are given as numbers and percentages. To test for differences between groups, we used the independent t test or one-way ANOVA (more than 2 groups) for continuous data and the χ^2 test for categorical data. Lastly, we performed ROC analyses to examine the discriminatory power of the indices to separate AD patients from normal elderly individuals and to examine whether qEEG could be used to separate patients with various dementia disorders from each other. The results of the ROC analyses are given as AUC, sensitivity, specificity, likelihood ratio for a positive test (LR+) and likelihood ratio for a negative test (LR-). The AUC should be significantly larger than 0.5 if the test (EEG) is better than what is achieved at random. The following formulas for LR+ and LR- were used: LR+ = probability of a positive result in a person with a disease/probability of a positive results in a person without the disease (true positive/false positive) = sensi-

Table 2. Characteristics of the participants included in the analyses

	Patients (n = 372)	Controls (n = 146)
Demographics		
Mean age ± SD, years	71.7 ± 8.6	66.5 ± 7.7
Female gender, n (%)	200 (54)	87 (60)
Married, n (%)	245 (66)	106 (74)
Education >9 years, n (%)	240 (65)	124 (85)
Primary clinical diagnosis-related dementia assessment, n (%)		
Healthy controls		146 (100)
Depression	12 (3)	
SCI	63 (17)	
MCI	121 (33)	
AD	135 (36)	
Vascular dementia	15 (4)	
LBD ^a	15 (4)	
Other dementias ^b	10 (3)	
Other comorbid diagnosis, n (%)		
Any heart disease	76 (20)	6 (4)
Diabetes	40 (11)	8 (6)
Previous stroke	20 (5)	1 (<1)
Previous or present depression	91 (24)	4 (3)
Use of drugs, n (%)		
Antipsychotics	9 (2)	1 (1)
Antidepressants	71 (19)	3 (2)
Tranquilizer/hypnotics	27 (7)	3 (2)
Anti-dementia drugs ^c	23 (6)	0
Pain killers	17 (5)	4 (3)

^a 10 with LBD and 5 with PDD.
^b 4 with frontal lobe dementia and 6 with dementias not specified.
^c 1 with memantine, otherwise acetylcholinesterase inhibitors.

tivity/1 – specificity; LR– = probability of a negative result in a person with a disease/probability of a negative results in a person without the disease (false negative/true negative) = 1 – sensitivity/specificity.

Ethical Considerations

In this study, we included healthy elderly individuals and patients with MCI or dementia at a very early stage. Thus, only persons with the capacity to consent to participation were included. All participants were given oral and written information, and they consented to participation in writing. The study was approved by the ethics committees in each of the 4 countries.

Results

The characteristics of the patients and the controls are shown in table 2. Except for education, no other demographic variable differed significantly between the two groups. The mean age of the female patients was 72.4 years (SD 9.2), and that of the men 71.0 years (SD 7.9; $p = 0.12$). The mean age of the female controls was 66.1 years (SD 7.8), and among the men it was 67.1 years (SD 7.2; $p = 0.48$). Comorbidities were more often observed in the patient sample than in the control sample, as was the use of psychotropic drugs that could possibly interfere with the EEG measurements. It should be noted that only 23 patients used anti-dementia drugs (first assessment at a memory clinic). Of the 10 individuals who used

Table 3. Cognitive performance of the participants

Clinical diagnosis	MMSE	CDT	CERAD-learning	CERAD-recall	CERAD-recognition
None (controls)	28.9 (1.3)	4.8 (0.5)	20.4 (4.0)	7.3 (1.7)	20 (1.4)
Depression	27.0 (4.0)	4.0 (1.6)	14.8 (5.8)	4.3 (2.5)	17.2 (2.7)
SCI	28.7 (1.3)	4.8 (0.5)	20.0 (3.9)	6.6 (2.3)	20.0 (1.5)
MCI	27.1 (2.1)	4.4 (1.0)	15.2 (4.3)	3.6 (2.3)	18.0 (2.0)
AD	23.3 (3.4)	3.7 (1.4)	11.0 (3.7)	1.5 (1.6)	15.8 (2.6)
Vascular dementia	22.7 (4.0)	3.3 (1.5)	11.6 (3.7)	1.9 (1.7)	16.3 (2.5)
LBD/PDD	24.1 (2.8)	2.8 (1.6)	11.5 (4.8)	3.4 (2.0)	17.4 (2.3)
Other dementias	24.3 (3.4)	3.6 (1.4)	12.2 (6.4)	2.7 (2.7)	18.0 (1.7)

Values are presented as means (SD).

Table 4. The crude probabilities of belonging to the group of normal healthy elderly individuals or the various clinical diagnostic groups by qEEG based on the SPR method, using the three indices

Clinical diagnosis	Healthy control index	AD index	DLB/PDD index
None (controls)	0.70 (0.22)	0.66 (0.24)	0.10 (0.12)
Depression	0.46 (0.28)	0.52 (0.30)	0.16 (0.23)
SCI	0.60 (0.25)	0.61 (0.23)	0.13 (0.13)
MCI	0.46 (0.28)	0.73 (0.25)	0.14 (0.15)
AD	0.24 (0.24)	0.70 (0.20)	0.24 (0.24)
Vascular dementia	0.22 (0.30)	0.77 (0.21)	0.19 (0.19)
LBD/PDD	0.07 (0.10)	0.39 (0.25)	0.77 (0.25)
Other dementias	0.32 (0.28)	0.74 (0.24)	0.21 (0.20)

The probabilities are given as means (SD). A value close to 1 indicates that the qEEG index can detect patients with a certain clinical diagnosis. The healthy control index is based on EEGs from healthy controls vs. patients with dementia, depression or substance abuse as derived from the database in Iceland by MentisCura. The AD index is based on EEGs from patients with AD vs. patients with all other dementia disorders. The DLB/PDD index is based on EEGs from patients with LBD/PDD vs. those with other dementias.

antipsychotics, 5 had dementia. With regard to antidepressants, the majority (n = 46) of the 76 patients who used this group of medication were not demented; 23 had AD.

The healthy controls and the patients with an SCI diagnosis performed similar on all cognitive tests, and these two groups did not differ statistically on any test results (table 3). The 12 patients with a primary diagnosis of depression had a cognitive function similar to that of the MCI patients. However, the amnesic MCI group (n = 57) differed from the nonamnesic group (n = 67) with regard to cognitive test results [mean MMSE 26.1 (SD 2.1) and 10-word CERAD-recall 1.6 (SD 1.2) vs. mean MMSE 28.0 (SD 1.7) and 10-word CERAD-recall 5.5 (SD 1.4); p < 0.001 for both measurements]. Otherwise, we found a significant decrease in test performance on all tests on the axis 'healthy controls/SCI-MCI/depression-dementia' (one-way ANOVA, p < 0.001 for all tests).

The mean depression score (maximum 10) among the patients was 1.97 (SD 2.1), compared to 0.1 (SD 0.5) among the controls (p < 0.001). In the clinical sample, the highest

Table 5. ROC analyses

Group comparisons	AUC (95% CI)	Sensitivity	Specificity	LR+	LR–
Healthy control index					
Healthy controls vs. all clinical patients	0.80 (0.76–0.84)	0.77	0.77	3.3	0.30
Healthy controls + SCI vs. all other patients	0.82 (0.78–0.85)	0.75	0.75	3.0	0.33
Healthy controls vs. AD patients	0.90 (0.86–0.94)	0.84	0.81	4.4	0.20
AD index					
AD patients vs. controls	0.54 (0.47–0.61)	NA	NA	NA	NA
AD patients <65 years vs. controls	0.69 (0.54–0.83)	0.70	0.65	2.0	0.46
AD patients vs. all other clinical patients	0.58 (0.53–0.65)	0.70	0.40	1.7	0.75
AD patients vs. other patients with dementia	0.57 (0.46–0.68)	NA	NA	NA	NA
DLB/PDD index					
DLB/PDD patients vs. controls	0.99 (0.97–1.00)	0.95	0.93	13.6	0.05
DLB/PDD patients vs. all clinical patients	0.95 (0.91–0.99)	0.87	0.87	6.7	0.15
DLB/PDD patients vs. other dementia patients	0.92 (0.86–0.98)	0.86	0.87	6.6	0.16
DLB/PDD patients vs. AD patients	0.92 (0.86–0.98)	0.85	0.87	6.5	0.17

NA = Not appropriate to calculate, as AUC does not differ from 0.5 (chance).

depression score was found among those with a diagnosis of depression [4.4 (SD 2.1)], followed by those patients with a diagnosis of LBD/PDD [3.1 (SD 1.8)] and SCI [2.5 (SD 2.4)]. The lowest score was found among the AD patients [1.4 (SD 1.9); one-way ANOVA, $p = 0.006$].

In table 4 we present the crude qEEG results, e.g. the probabilities for the controls and each of the clinical diagnostic groups of belonging to the healthy control group, the AD group or the group of patients suffering from either DLB or PDD based on the SPR method. The 10 patients with LBD did not differ from the 5 patients with PDD (data not shown), and we therefore treated them as one group to have more subjects in this group, which has been done in several studies. The amnesic MCI group did not differ from the nonamnesic MCI group on any of the three indices, and we therefore did not make separate analyses for the two MCI groups in the further analyses. The 15 patients with a diagnosis of LBD or PDD differed markedly and significantly ($p < 0.001$) from the other dementia patients on all three indices (table 4).

The results of the ROC analyses are shown in table 5. Besides reporting the AUCs, we added the sensitivity and specificity for situations where the sensitivity should be $\geq 70\%$. Two of the ROC analyses are shown as ROC curves in figure 1 to illustrate the main findings.

Discussion

This is the first study of this extent that uses the SPR method to analyze qEEGs for the differential diagnosis of individual patients with a user-friendly composite score extracted from multiple qEEG features. By including patients recruited from everyday clinical practice at 6 Nordic memory clinics, we found that qEEG, using the SPR method, was very useful in separating patients with LBD or PDD from all other clinical patients regardless of their cognitive status and diagnosis. We further found that the EEG method separated patients with AD from normal controls but did not separate patients with AD from those with other dementia disorders, except for DLB/PDD. The method poorly separated patients with AD from those with MCI, which could be expected, as a proportion of individuals with MCI are in fact in an early stage of AD.

Fig. 1. **a** ROC analysis of qEEG using the healthy control index to separate controls from AD patients. **b** ROC analysis of qEEG using the DLB/PDD index to separate DLB/PDD patients from other demented patients.

In the ROC analyses, the SPR method using the DLB/PDD index distinctly separated the DLB/PDD patients from the AD patients, the other patients with and without dementia and the controls. AUCs >0.9, a high sensitivity, specificity and LR+ as well as a low LR– all indicate that the method is valid. The study by Snaedal et al. [25] from the Memory Clinic in Iceland reported similar results, but no information on the cognitive status of the patients was given. In the present study, the DLB/PDD patients were in the stage of early dementia, with MMSE scores of 24.1 ± 2.8 points. Other studies support our findings that the qEEG characteristics of DLB/PDD patients differ from those of patients with other dementias [19, 38, 39]. The most probable reason for this convincing result is that qEEG using the SPR method captures the specific EEG pattern of LBD and PDD. It would be of interest to know if this typical EEG pattern is also present in the preclinical stage of LBD. The present study cannot answer this question. However, a recently published follow-up study of MCI patients showed that qEEG was able to predict the development of LBD [39].

Using the healthy control index – which is based on qEEGs from healthy controls versus patients with dementia, depression or substance abuse from the Icelandic database – the SPR method well separated the controls from the patient groups and the specific group with a diagnosis of AD. The study by Snaedal et al. [25] came to the same conclusion, but with statistically better results. The results can be seen as a ‘proof of concept’ of the SPR method and may indicate that this method, measuring the electrophysiology of the brain, can be used in order to increase diagnostic certainty when diagnosing the causes of dementia.

Using the AD index, which is based on EEGs from patients with AD versus those with all other dementia disorders, the SPR method did not significantly separate AD patients from other patients with dementia. Younger AD patients were separated from normal controls and from other younger clinical patients in a significant way, although the discriminatory power was not perfect, as expressed by the low AUC and LR+ and the high LR–. These results are in accordance with those of a previous study by Ommundsen et al. [24], which also included an unselected group of memory clinic patients. This result might be seen as beneficial, since

younger patients with AD more often have atypical clinical presentations and are generally much harder to diagnose than older patients with AD.

This study can be compared with the study by Ommundsen et al. [24], as both used the EEG SPR method in the same way to evaluate individual EEG registrations on the basis of a database that had been formed earlier, not including any of the same cases. The study by Snaedal et al. [25] used the method in a different way, i.e. to separate several clinical groups and controls, thereby creating a database on the basis of their difference in EEG features the other studies rely on. This could be the main reason for the more favorable results of that study.

Use of psychotropic drugs and comorbid disorders, especially brain disorders, could have influenced the EEG recordings and thereby biased the results. In the present study, less than half of the patients used such drugs, and less than half of them had comorbid disorders. The EEG recordings could therefore have been influenced only to some degree. However, our sample represents patients who typically are referred to a memory clinic, and we have to take into consideration that these patients could have comorbid disorders that possibly influence all the examinations that are applied in a dementia workup. In this study, we wanted to test the value of qEEG among typical memory clinic patients, not a sample of selected patients.

The study has limitations. Although at least 2 experienced physicians made the clinical diagnoses at each center, we cannot rule out that some patients had been falsely diagnosed. Most patients with dementia were in an early stage of disease, and diagnoses at this stage can be difficult to make. This is also the case for the distinction between dementia and MCI, where only a follow-up of the patients could reveal progression to dementia. Secondly, we did not use all biomarkers that are available today in all patients, only as indicated according to routine clinical practice. Some patients may have received a false diagnosis for this reason. The strengths of the study are the fairly large number of patients and controls included and that the patients were included in an unselected manner, recruited from everyday clinical practice. A further strength is that the patients were examined in a standardized manner with a harmonized protocol, since it was performed in centers that have been participating in the NIDD in recent years, harmonizing their diagnostic workups.

To sum up, only two studies on qEEG using the SPR method have been published that include patients from everyday practice: the present one and the study by Ommundsen et al. [24]. Using clinical diagnoses as the gold standard, our study showed that the SPR method was excellent in discriminating DLB/PDD patients from both healthy controls and patients with other dementia disorders but poor in discriminating between AD patients and patients with other clinical diagnoses. The method well separated normal controls from those with dementia, including AD. Other previously reported studies on the use of this method showed more favorable results, but they had been conducted using the SPR method to separate groups, not to examine individuals [23, 25].

Further longitudinal studies of MCI patients followed up clinically in the same standardized way as within the NIDD should be conducted to examine if this qEEG method could separate patients with LBD from AD patients in a preclinical phase – as has been done in a recent Italian study [39]. Furthermore, the method should be compared to other biomarkers of degenerative disorders of the brain, first and foremost AD, as the current project indicates that EEG could add to the diagnostic arsenal in cognitive impairment and dementia. The method is cheap, noninvasive and simple to use and can be applied outside academic centers; also, there is a need for diagnostic methods that can be applied more widely than PET, MRI and spinal fluid marker assessment.

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Disclosure Statement

None of the authors have any conflicts of interest to declare.

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