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The Power of EEG to Predict Conversion from Mild Cognitive Impairment and Subjective Cognitive Decline to Dementia

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Keywords
Mild cognitive impairment · Subjective cognitive decline · Dementia · EEG

Abstract
Introduction: The aim of this study was to examine if quantitative electroencephalography (qEEG) using the statistical pattern recognition (SPR) method could predict conversion to dementia in patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). ***Methods:*** From 5 Nordic memory clinics, we included 47 SCD patients, 99 MCI patients, and 67 healthy controls. EEGs analyzed with the SPR method together with clinical data recorded at baseline were evaluated. The patients were followed up for a mean of 62.5 (SD 17.6) months and reexamined. ***Results:*** Of 200 participants with valid clinical information, 70 had converted to dementia, and 52 had developed Alzheimer's disease. Receiver-operating characteristic analysis of the EEG results as defined by a dementia index (DI) ranging from 0 to 100 revealed that the area under the curve was 0.78 (95% CI 0.70–0.85), corresponding to a sensitivity of 71%, specificity of 69%, and accuracy of 69%. A logistic regression analysis showed that by adding results of a cognitive test at baseline to the EEG DI, accuracy could improve. ***Conclusion:*** We conclude that applying qEEG using the automated SPR method can be helpful in identifying patients with SCD and MCI that have a high risk of converting to dementia over a 5-year period. As the discriminant power of the method is of moderate degree, it should be used in addition to routine diagnostic methods.

Introduction

The World Health Organization has declared dementia to be one of the biggest health challenges in the future to come because neurodegenerative disorders are the most prominent underlying conditions in which no modifying

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treatment exists [1]. Due to the increasing number of older people worldwide, the prevalence of dementia will increase from about 45 million people today to >130 million during the next 30 years [2, 3]. Alzheimer disease (AD) is the most frequent cause of dementia followed by vascular dementia (VaD), dementia with Lewy bodies (DLB), and other forms of neurodegenerative disorders. Typically, AD develops slowly, and brain pathology can be found decades before clinical symptoms are seen in patients [4]. If or when we find modifying treatments, such treatments should be initiated before the disease has progressed to a clinical state with severe cognitive decline and impaired function in activities of daily living. Therefore, it is of importance to find valid biomarkers that could identify people that have a high risk of developing dementia and, preferably, the underlying cause of dementia.

Prior to the stage of dementia, 2 stages of impaired cognition are frequently defined: subjective cognitive decline (SCD), a stage of subjectively experienced impaired cognition, which is not supported by an informant or by neuropsychological testing, and mild cognitive impairment (MCI), which is supported by an informant and in-depth testing. In both stages, the individuals are able to perform personal as well as instrumental activities of daily life, but they are at high risk of developing dementia [5–8]. Using standardized criteria, these individuals can be identified [9–14]. Previous studies have shown that 20–50% of people with MCI will convert to dementia [6–8, 15]. Older age, poorer cognition, APOE ε4 allele carrier status, and hypertension are found to increase the conversion rate to dementia [15]. The use of various MRI and PET methods and cerebrospinal fluid (CSF) examination, measuring concentrations of amyloid-β, phosphorylated and total tau proteins, as well as other proteins, including inflammatory markers, have shown to be helpful in predicting patients with MCI and SCD who will convert to dementia, especially to AD [16–22]. A recent Cochrane review, however, does not support the use of β-amyloid PET as biomarker for AD, but studies examining the combination of cognitive tests with CSF proteins, MRI, and FDG-PET have shown excellent results in identifying people with MCI that would convert to dementia [23–25]. However, the use of biomarkers are time and personnel consuming, costly, and some of them are invasive, and, consequently, not ideal for use in daily clinical practice, except in subspecialized settings. Therefore, biomarkers are generally not used in primary care settings and not at all in countries with poor economy, and some will not be applied where doctors are reluctant to use invasive methods such as tapping cerebrospinal fluid. Electroencephalography (EEG), on the other hand, is a low-cost, noninvasive, simple examination that can be used in most clinics and even in primary care settings, especially if an automatic reading method is applied. In the last decade, studies were published which examined the power of EEG to detect those persons with MCI that will convert to dementia [26–30]. Further, our Nordic group has examined the validity of automated quantitative EEG (qEEG) using the statistical pattern recognition (SPR) method, and various results have demonstrated how this method can be used to separate patients with dementia from healthy controls (HC) [31–37]. Especially, qEEG seems to be helpful in diagnosing DLB [29, 35, 38, 39]. The SPR method has, however, never been applied to examine if the method can be used to separate patients with SCD and MCI that will later convert to dementia or not. Thus, the aim of this study was to examine if qEEG using the SPR method could predict conversion to dementia in patients with SCD and MCI.

Material and Methods

This an observational longitudinal study including patients visiting 5 memory clinics in 3 Nordic countries. The maximum follow-up time was 7 years, and mean follow-up time was 62.5 (SD 17.6) months.

Participants

From a previous qEEG validity study in 6 Nordic clinics, consisting of 377 patients and 146 HC, we included all patients with a diagnosis of SCD and MCI from 5 of those clinics [35]. Patients with a primary diagnosis of depression of moderate or severe degree, bipolar disorder, or a psychotic disorder were excluded. In addition, we at random included a group of HC from the previous study. This resulted in 47 patients with SCD, 99 with MCI, and 67 HC, a total of 213 participants. The participating sites were the university memory clinics in Oslo and Bergen (Norway), Copenhagen and Roskilde (Denmark), and Reykjavik (Iceland). For 13 patients, we could not retrieve valid follow-up data because of death or because the participants declined reexamination. Among these, the diagnosis was SCD in 2 and MCI in 11 patients. They did not differ regarding age, gender, education level, marital status, or cognition compared to the included SCD and MCI patients. Thus, the analyses were made with data from 200 participants, 45 with SCD, 88 with MCI, and 67 HC.

Assessments

A comprehensive clinical assessment was conducted at baseline and follow-up, except for those patients who had died during follow-up and for a few patients residing in nursing homes because of dementia of moderate or severe degree. For those, hospital and nursing home records were examined. The assessment was similar at the 5 academic centers and included a history from the

patient and an informant, a physical examination, blood tests to screen for disorders associated with cognitive decline, neuropsychology to cover various cognitive domains, CT or MRI of the brain for evaluation of general atrophy and atrophy of the medial temporal lobes (MTA by Scheltens' scale [40]), and white matter changes according to the scale of Fazekas et al. [41]. Depression was assessed using a modified version of the Montgomery-Aasberg Depression Rating Scale [42]. At baseline, each of the 10 items was assessed as present or absent, giving a minimum score of 0 and a maximum score of 10. At follow-up, the full scoring procedure was used with a minimum score of 0 and a maximum of 60 [42, 43]. If the basic assessment was not sufficient to make a diagnosis, lumbar puncture was done for examination of β-amyloid, total tau, and phosphorylated tau protein in cerebrospinal fluid, and/or FDG-PET or DaTScan were carried out.

The following cognitive tests were used in the analyses:

- The Mini Mental Status Examination, a test that has a minimum score of 0 and a maximum of 30 (a higher sore indicates better cognitive function) [44, 45];
- The clock drawing test (CDT), using the scoring instruction of Shulman [46], with a minimum score of 0 and a maximum score of 5 (a higher score indicates better function);
- The 10-word test of the Consortium to Establish Alzheimer Disease Registry (CERAD), using all 3 scorings: CERAD learning with a maximum score of 30, CERAD recall with a maximum score of 10, and CERAD recognition with a maximum score of 20 [47] (a higher score on each indicates better cognition).

Details on the comprehensive assessment, which was similar in the clinics, can be found elsewhere [48].

Diagnoses of the Clinical Sample

Clinical diagnoses were made by at least 2 experienced physicians. MCI was diagnosed using the MCI criteria of Winblad et al. [10]. In patients referred to the memory clinic because of cognitive complaints who did not meet the Winblad criteria or criteria for dementia, the diagnosis was SCD, using criteria similar to those made by Jessen et al. [12]. At follow-up, AD was diagnosed according to the criteria established by McKhann et al. [49], whereas VaD was diagnosed by the NINDS-AIREN criteria, DLB according to the revised consensus criteria, and frontotemporal dementia by the Lund-Manchester criteria [13, 49–52]. Dementias due to Parkinson disease were diagnosed according to the ICD-10 criteria [14]. Other dementia was used for unspecified dementia and dementia due to causes such as normal pressure hydrocephalus and dementia due to multiple sclerosis. All diagnoses were made independently of the qEEG results.

Healthy Controls

Details of HC recruitment are described in the previous paper [35]. They were interviewed, a history of previous and present disorders and use of drugs were recorded and tested with the MMSE, the CDT, and the CERAD-10 word test. Depression was assessed with the Montgomery-Aasberg Depression Rating Scale in the same way as in the patients. Persons with a result on a cognitive test below 1 SD according to their age were excluded at baseline. At follow-up, they were examined comprehensively according to the standard set in the memory clinic if MCI or dementia was suspected.

EEG Recordings

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

qEEG Data Analysis

The specific section of each recording chosen for further processing was selected by a trained technician such that artifacts were minimal and the length of the section at least 150s. Prior to feature extraction, the chosen segment was preprocessed by applying a 8th-order Butterworth band-pass filter with the chosen band (0.1–70 Hz) to eliminate potential low- and high-frequency disturbances from the signal. The features extracted from the EEG recording and used in the evaluation of the dementia index (DI) were retrieved according to the recommendations of the Pharmaco-EEG society [53]. The society recommends that the signal is segmented into 2-s segments overlapping by 1 s. The signal is then analyzed segment by segment, and the feature values are estimated by evaluating the expected value over all the segments. This can be achieved by various means. For instance, using the average value or an alternative robust measure. Using a robust measure minimizes the impact of outliers and hence reduces the influence of potential signal artifacts. We use the simplest robust estimate, that is, the median of the feature values. The features used are all related to the spectral properties of the recording. Discrete fast Fourier transform is applied to estimate the spectral properties of the signal [54]. The analysis relies on recordings from 19 electrodes. The electrodes used are named according to the international 10-20 system [55]: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. If the fast Fourier transform components for each of the electrodes, segments, and discrete frequencies considered are denoted by σ_{cij}, where $c \in \{1,2,\ldots, 19\}$ indicates the channel, $i \in \{1,\ldots, N\}$ the segment of the N segments considered, and $j \in \{1,\ldots, 90\}$ the discrete frequencies (0.5, 1,…, 45 *Hz*), the full spectral resolution covariance between channels c and k is then expressed by $x_{ck}^{ij} = \sigma_{cij} \times \sigma_{kij}^{*}$. These covariances constitute the base features used for analysis and evaluation of the classification index values. To determine the core features relied on, principal components (PCs) were determined based on the Mentis Cura database of EEG recordings. PC analysis was performed on data from dementia subjects in the database. This was done separately for each covariance. PCs were then ranked according to their individual discriminatory properties in separating the subjects in the database. The discriminatory properties were determined according to the area under curve (AUC) of the receiver-operating characteristic curve (ROC). We use the 2 best performing components from each of the covariances to extract the core features used for evaluation of the index. If $P_{ck\alpha j}$ denotes the 2 chosen PCs, $\alpha \in \{1, 2\}$, for electrode pair (c, k) at frequencies $j \in \{1,\ldots, 90\}$, the core features considered for analysis then become $C_{ck\alpha} = E_i \{\sum_{j=1}^{90} x_{ck}^{ij} P_{ck\alpha j}\}$. Figure 1 illustrates typical examples of the PCs for 1 covariance, P_{111j} and P_{112j}, which describe how the spectral bands are weighted for the analysis. The PCs can be related to the classical EEG power bands, δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–30 Hz), which are indicated in the figure. Then PC1 corresponds to the difference between the combined δ and θ power and the β power, while PC2 is a weighted measure of the total power

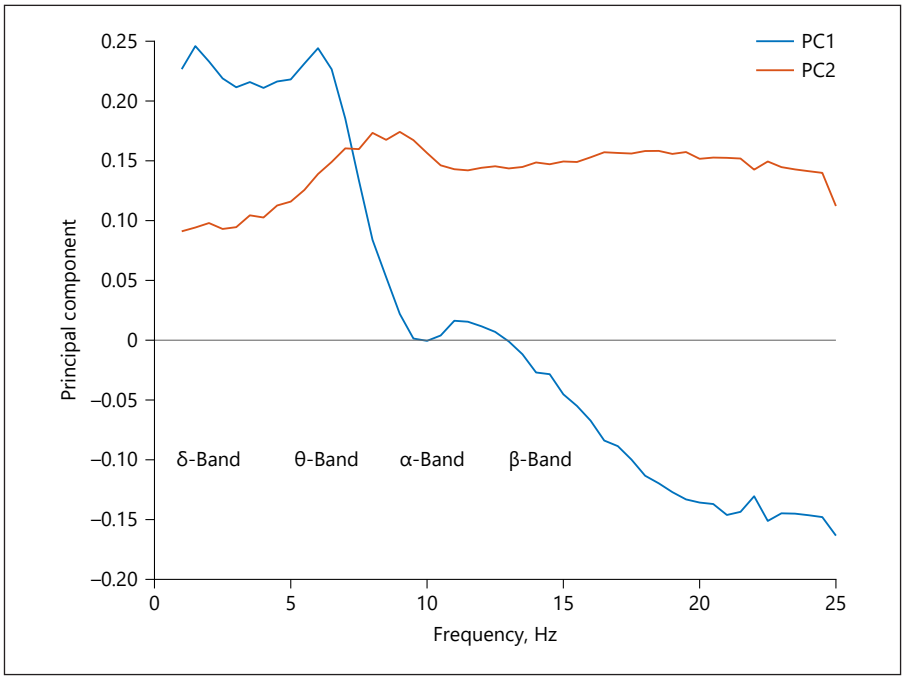


Fig. 1. Typical examples of the PCs for one covariance, P_{111j} and P_{112j} specifically. The classical EEG power bands δ, θ, α, and β are indicated. In terms of the classical bands, PC1 corresponds to the difference between the combined δ and θ power, and the β power, while PC2 is a weighted measure of the total power.

Table 1. Baseline characteristics of the 200 participants according to diagnosis at baseline

	All (n = 200)	HC (n = 67)	SCD (n = 45)	MCI (n = 88)	p value
Female	105 (53%)	37 (55%)	24 (53%)	44 (50%)	0.800[a]
Married	150 (75%)	49 (73%)	34 (76%)	67 (76%)	0.800[a]
Age, years	68.7±8.2	65.6±7.3	68.0±8.0	71.2±8.1	<0.001[b]
Education, years	12.3±3.9	13.4±3.5	12.9±3.8	11.2±4.0	0.001[b]
MMSE	28.0±2.0	29.0±1.1	28.7±1.2	27.0±2.2	<0.001[b]
CDT	4.6±0.8	4.7±0.5	4.8±0.6	4.4±1.0	0.003[b]
CERAD recall	5.2±2.8	7.3±1.8	6.4±2.0	3.4±2.3	<0.001[b]

Numbers (%) and means ± SD are shown. [a] χ^2 test, [b] One-way ANOVA.

with slightly more emphasis on α and β power. The index value for an individual recording is evaluated from these features by $I = \Sigma_{ck\alpha}C_{ck\alpha}\beta_{ck\alpha} + \beta_1^A A + \beta_2^A A^2 + \rho$, where A is the age of the subject in years. The classification coefficients $\beta_{ck\alpha}$, β_i^A, and ρ were determined using a combination of genetic algorithms to optimize the number of features used, and SVM (support vector machine), an SPR, was applied in the Mentis Cura database, which contains EEG data from people with various dementia diagnoses and HC. This was done separately for men and women, resulting in separate gender-dependent indices. It should be noted that the DI was developed to separate people with dementia from nondemented subjects and not to predict conversion from MCI to dementia.

Statistics

All data were analyzed using SPSS software. The DI data were close to normally distributed. To test for differences between groups, we used the independent t test or one-way ANOVA (>2 groups) for continuous data. χ^2 and Fisher exact test were used to compare groups for categorical data. The paired sample t test was used to test for differences between baseline and follow-up cognitive test scores for converters and nonconverters, separately. Spearman's ρ and linear regression analysis were used to examine variables associated with the DI. Logistic regression analysis was used to examine predictors of conversion to dementia. We did 2 separate analyses because the correlation between MMSE and CERAD recall was as high as 0.6. As the 3 different scorings of the CERAD10 word test correlated highly (CERAD learning vs. recall 0.79), we only used the CERAD recall score in the linear regression analyses as this is a measure of episodic memory. ROC analysis was applied to examine the discriminatory power of the DI to separate patients that converted to dementia from those who did not. We calculated the AUC, sensitivity, specificity, the likelihood ratio for a positive test, and the likelihood ratio for a negative test, and the cutoff of the DI that gave the best classification with a sensitivity of approximately 70%. AUC should be significantly larger than 0.5 if the test (qEEG) is better then what is achieved by random. The likelihood for a

Table 2. Participants (*n*) from different diagnostic groups at baseline that converted to dementia, declined, remained stable, or recovered

Baseline	Status at follow-up after a mean of 62.5 months				
	normal	SCD	MCI	dementia	dementia diagnosis
HC (*n* =67)	62 (92.5%)	3 (4.5%)	1 (1.5%)	1 (1.5%)	AD = 1
SCD (*n* = 45)	8 (18.0%)	24 (53.0%)	6 (13.0%)	7 (16.0%)	AD = 5, FTD = 1, OD = 1
MCI (*n* = 88)	2 (2.0%)	2 (2.0%)	22 (25.0%)	62 (71.0%)	AD = 47, FTD = 1, DLB/PD = 3, VaD = 3, mixed AD/VaD = 4, OD = 4

Numbers are shown. AD, Alzheimer disease; DLB, dementia with Lewy bodies; FTD; frontotemporal dementia; OD, other dementia; PD, Parkinson disease; VaD, vascular dementia.

Table 3. Characteristics at baseline and follow-up of the 130 nonconverters compared to the 70 converters

Characteristics	Baseline			At follow-up		
	nonconverter	converter	*p* value	nonconverter	converter	*p* value
Cognition						
MMSE score	28.8±1.5	26.8±2.1	<0.001	28.5±3.2	21.8±4.8	<0.001
CDT score	4.7±0.7	4.3±1.0	<0.001	4.8±0.6	3.2±1.4	<0.001
CERAD recall score	6.6±2.3	2.9±2.0	<0.001	6.7±2.1	1.1±1.5	<0.001
Comorbidity						
Hypertension	52 (40%)	40 (56%)	<0.05	47 (39.5%)	24 (41%)	ns
Any heart disease	13 (10%)	16 (22.5%)	<0.05	20 (17%)	15 (25.5%)	ns
Diabetes	6 (5%)	6 (8.5%)	ns	6 (5%)	5 (8.5%)	ns
Depression	18 (14%)	13 (18%)	ns	1 (1%)	17 (29%)	0.01
Use of drugs						
Antipsychotics	3 (2%)	0 (0%)		0 (0%)	0 (0%)	
Antidepressants	11 (8.5%)	16 (22.5%)	<0.01	10 (9%)	8 (17%)	
Hypnotics/tranquilizer	7 (5%)	6 (8.5%)		6 (5.5%)	0 (0%)	
Antidementia drugs	0 (0%)	2 (3%)		1 (1%)	16 (22.5%)	

Numbers (%) and means ± SD are shown. The independent *t* test was used for continuous variables and the χ^2 or Fisher exact test for categorical variables. Due to the small numbers of drugs, statistical analysis was not done. Intragroup comparisons (baseline vs. follow-up) were performed using paired sample *t* test but are not shown. $p = 0.8$, 0.9, and 0.7 for MMSE, clock drawing test, and CERAD recall scores at baseline vs. follow-up, respectively, for nonconverters, and $p < 0.001$, $p < 0.001$, and $p < 0.002$ for converters, respectively. ns, nonsignificant.

positive test = 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) = sensitivity/1 – specificity. The likelihood for a negative test = 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. Accuracy was defined as the proportion of correctly classified participants (converters + nonconverters).

Results

Table 1 shows the baseline characteristics of the study participants. As can been seen, the MCI patients were significantly older, had less years of education, and had poorer cognition as measured by MMSE, CDT, and CERAD10 recall compared to the participants of the 2 other groups. It should be noted that 45 (45%) of the MCI patients had a score between 28 and 30 on the MMSE, and 33 (33%) had a score between 5 and 10 on CERAD recall.

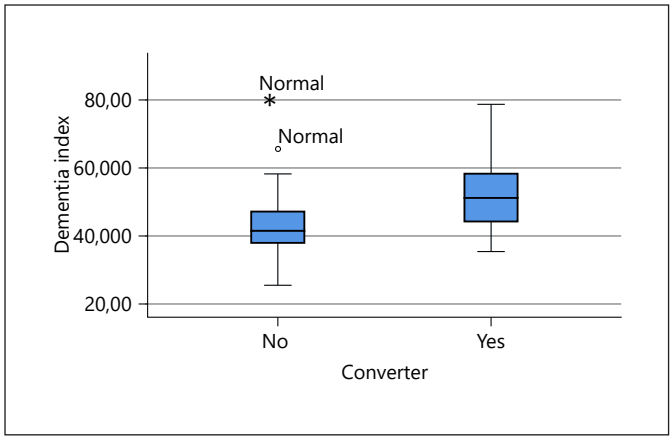
Conversion to Dementia

At follow-up, 70 of 200 (35%) had converted to dementia, 62 MCI patients (71%), 7 with SCD (16%), and 1 HC (1.5%). The converters were significantly older (73.1 [SD 7.5] years), compared to nonconverters (66.1 [SD 7.5] years) and had less years of education (11.2 [SD 4.3] vs. 13.0 [SD 3.6] years). No difference was found between

Table 4. Dementia index (mean ± SD) at baseline among nonconverters and converters

	Dementia index
All (n = 200)	46.9±9.9
Nonconverters (n = 130)	42.6±9.9
Converters	
0–12 months (n = 25)	58.7±10.9
13–24 months (n = 16)	51.4±11.9
25–36 months (n = 14)	48.1±7.7
37–48 months (n = 6)	47.8±6.8
49–60 months (n = 8)	48.0±4.7

$p < 0.001$, nonconverters vs. converters (t test). Comparison between the 5 groups of converters: ANOVA $p = 0.0001$. For 1 converter we did not have exact information at the time to conversion.



Color version available online

Fig. 2. Box plot of the dementia index at baseline for the group who converted (yes) and the group who did not convert to dementia (no) during follow-up.

gender as 51% converters and 53% nonconverters were women, and 77% converters were married versus 72% nonconverters. Details of the diagnostic status at follow-up can be found in Table 2, whereas Table 3 shows that the converters had poorer cognitive test scores than nonconverters both at baseline and follow-up and poorer cognition at follow-up compared to baseline, whereas that was not the case for the nonconverters. Time to conversion was <1 year for 25 patients and <2 years for 41 (Table 4).

EEG DI Using SPR and Its Associates

The baseline DI for the MCI patients was 49.8 (10.0), for the SCD 44.8 (9.7), and for the HC 41.9 (8.2). For the converters, the index at baseline was 52.1 (SD 10.4) versus 42.6 (SD 9.9) among the nonconverters (Fig. 2).

The highest correlation with the DI was found for age, 0.66 ($p < 0.001$), followed by the CERAD recall score at baseline, –0.45 ($p < 0.001$), MMSE score at baseline, –0.41 ($p < 0.001$), years of education, –0.27 ($p < 0.001$), and CDT score at baseline, –0.14 ($p = 0.012$). A linear regression analysis, with the qEEG DI as the dependent variable and gender, age, education, MMSE score, and converters versus nonconverters as independent variables revealed that age ($p < 0.001$), MMSE score at baseline (0.02), and being a converter ($p = 0.004$) were significantly associated with the DI. Educational level was not. Applying the CERAD recall score instead of MMSE at baseline showed that age ($p < 0.001$), gender ($p = 0.02$), CERAD recall ($p = 0.02$), and being a converter ($p = 0.04$) were significantly associated with the DI.

Table 5 shows the qEEG DI for various age groups, educational levels, gender, MMSE score, and CERAD recall score for nonconverters and converters, separately. The index for those who developed AD was 52.5 (SD 4.6), for VaD 54.9 (SD 3.1), for mixed AD/VaD 52.5 (SD 4.6), for DLB/Parkinson disease 46.5 (12.6), for frontotemporal dementia 41.6 (SD 8.7), and for the other dementia group 50.5 (7.7). The DI was highest for those who converted within the first or second year after the baseline examination (Table 4). For patients who converted to AD within 2 years, the DI was 56.5, whereas it was 46.6 for those who converted after 2 years.

The Power of the DI to Separate Converters from Nonconverters

The results of the ROC analyses revealed that the DI had moderate power to separate the converters from nonconverters regardless if all participants were included, those who converted to dementia within the 2 first years, or those who developed AD (Table 6). Logistic regression analysis using converters versus nonconverters as dependent variable and DI, MMSE score, age, gender, and education showed that both the MMSE score (OR 0.62, 95% CI 0.49–0.79, $p < 0.001$) and the DI (OR 1.1, 95% CI 1.002–1.13, $p = 0.005$) were significant predictors of conversion to dementia with a correct classification rate of 78%. Replacing the MMSE score with the CERAD recall score at baseline, the CERAD recall (OR 0.56, 95% CI 0.46–0.68, $p < 0.001$), and the DI (OR 1.06, 95% CI 1.02–1.12, $p = 0.04$) significantly predicted dementia with a correct classification rate of 84%.

Table 5. Dementia index (mean ± SD) associated with gender, age group, educational level, MMSE, and CERAD recall score at baseline

	All	*p* value	Nonconverters	*p* value	Converters	*p* value
Gender						
Female	50.7±9.7	0.8	42.8±9.1	0.8	55.0±10.4	0.02
Male	48.5±14.7		42.4±5.8		49.2±9.9	
Age groups						
<65 years	39.7±7.7	<0.001	39.3±8.2	<0.001	42.3±4.7	0.004
>65 years	48.8±9.6		44.7±6.6		53.5±10.4	
Education						
<10 years	50.7±12.5	<0.001	46.2±12.1	0.03	55.2±12.2	0.09
>10 years	44.9±8.8		41.9±6.6		50.7±9.2	
MMSE score						
<27	54.2±9.8	<0.001	51.2±2.7	0.002	57.2±10.0	0.002
>27	44.4±9.0		42.1±7.7		49.2±9.6	
CERAD recall						
0–4	51.4 10.1	<0.001	49.3±11.9	0.006	52.2±10.6	0.8
5–10	43.0±8.4		41.8±7.6		50.0±9.3	

Table 6. ROC analysis of EEG dementia index (DI) as predictor of conversion to dementia

	AUC (95% CI)	SS, %	SP, %	Accuracy, %	LR+	LR–	DI cutoff
Conversion including all participants	0.78 (0.70–0.85)	71	68	69	2.2	0.43	44.8
Conversion within the first 2 years	0.79 (80.73–0.86)	70	70	70	2.3	0.43	47.3
Conversion to AD	0.78 (0.71–0.84)	71	68	69	2.2	0.43	44.8
Conversion to AD, VaD, or mixed AD/VaD	0.79 (0.73–0.86)	73	70	71	2.4	0.39	45.3
Conversion from SCD to dementia	0.83 (0.64–1.0)	67	64	65	1.9	0.52	46.6
Conversion from MCI to dementia	0.78 (0.70–0.85	69	71	70	2.4	0.44	45.8

AD, Alzheimer disease; AUC, area under the curve; LR+/LR–, positive/negative likelihood ratio; MCI, mild cognitive impairment; SCD, subjective cognitive decline; SP, specificity; SS, sensitivity; VaD, vascular dementia.

Discussion

To our knowledge, this is the first study on the discriminatory power of qEEG using the fully automated SPR method to predict conversion from SCD and MCI to dementia. It turned out that using the qEEG DI, the discriminatory power was of moderate degree, corresponding to a sensitivity of 71%, specificity of 68%, and accuracy of 69%. It is difficult to compare our results with those of other EEG studies that have examined the power of EEG to predict conversion as the populations differ in size and cognition, the analytic methods differ, and ROC analyses have not always been done [26–30]. However, Poil et al. [26] could report a sensitivity of 88% and specificity of 87% applying several β-related frequencies (13–30 HZ), whereas Moretti [27] found the α3/α2 frequency power ratio corresponded well with MRI findings indicating AD. Bonanni et al. [29] found that qEEG was perfect to predict DLB, with a sensitivity and specificity of 100%. The fact that the DI was developed by cross-sectional analysis rather than by longitudinal follow-up could explain the modest discriminatory power.

The question arises whether a diagnostic test with a sensitivity of 71% and a specificity of 68% should be used in daily clinical practice. The DI should not be recommended as a prognostic instrument alone, neither in all participants nor in a subset of the participants (converting to AD or converting after 2 years). However, the EEG DI was associated with being a converter in the linear regression analyses, and in the logistic regression analysis the DI together with cognitive performance at baseline significantly predicted conversion to dementia, suggest-

ing that both analyses indicate that the DI has an additional value in predicting conversion to dementia. In logistic regression analyses, we found that both MMSE and CERAD recall, when analyzed together with the DI, significantly predicted the conversion to dementia, whereas introducing medial temporal lobe atrophy measurements did not improve the results. The combination of CERAD recall and DI classified 84% of the participants correctly, whereas this rate was 78% for the combination of MMSE and DI. The better performance of the CERAD recall in combination with the DI than the MMSE is probably due to a ceiling effect using the MMSE, as 45% of the MCI patients scored above 27 on the MMSE. Another explanation could be that CERAD recall is more sensitive and primarily a test for episodic memory whereas MMSE measures cognition in more general terms. Episodic memory is the cognitive function that in most cases declines early in the development of AD, the most frequent dementia disorder in the present study. Moreover, a systematic review made by the Cochrane group revealed that the MMSE is not a valid marker of conversion from MCI to dementia [56]. But, the results from the logistic regression analyses should be interpreted with caution as the cognitive tests and MRI were used in the diagnostic assessment.

It is difficult to compare our results with studies examining MRI, FDG and amyloid PET, and CSF biomarkers as predictors of conversion to dementia, because different populations and different statistical methods are used. Recently, one study using a machine learning program to evaluate structural brain changes using MRI as predictors of conversion reported very high AUC, and another study using voxel-based FDG-PET also reported very good results [19, 21]. Best results are though reported from studies using various biomarkers in combination [24, 25]. However, to design a study to examine the discriminant power of a combination of biomarkers and a cognitive test is difficult due to a circularity problem. We cannot examine the discriminant power of a test or examination when the result of the same is used together with tests to make a valid etiological diagnosis of dementia.

In the present study, as much as 71% of the MCI patients converted to dementia through a mean observation period of 5 years, whereas 25% were stable, and 4% improved. Of the SCD patients, 16% converted, 53.6% were stable, and the remaining 31.4% recovered (Table 2). Even with an observation time up to a maximum of 7 years, we consider that the rate of conversion was high for both the MCI and SDC group, and higher compared to most published studies [15]. The reason might be that the patients of the present study are referred to an academic clinic. In the Nordic countries, except for the larger cities in Denmark, primary care physicians usually assess, diagnose, and treat patients with typical signs of dementia, and refer only the more complicated patients to memory clinics [57–60]. It should also be noted that converters to dementia in this study had more often poor cognition and hypertension, and were older as compared to nonconverters (Table 3), which are risk factors for conversion, as reported in systematic reviews [15]. Further, converters had significantly higher consumption of antidepressants at baseline than nonconverters (Table 3), which indicates some predementia psychiatric symptoms.

Limitations

The study has the following limitations. Although at least 2 experienced physicians at each center made the clinical diagnoses, it is possible that some patients should have been given another diagnosis. We applied current clinical criteria for the diagnosis of SCD and MCI, but it is not always simple to separate patients with MCI from those with an early phase of a dementia disorder. In a clinical setting, as in the present study, patients with an unsecure diagnosis are followed up. All patients had either a CT or MRI examination, but not all had CSF and PET examination, which could have improved the diagnostic accuracy. However, by inspecting the MMSE, CDT, and CERAD recall scores (Table 1), most included SCD and MCI patients had good cognitive function at baseline, which renders a diagnosis of dementia at baseline unlikely. In addition, the converters had a significant decline in all 3 cognitive tests at follow-up, whereas the nonconverters did not decline at follow-up (Table 3). These findings strengthen our belief that the clinical diagnoses were correct both at baseline and at follow-up. Further strengths of the study are the fairly large number of patients and HC and that the patients were included in an unselected manner, recruited from everyday clinical practice.

Conclusion

qEEG using the automated SPR method can be helpful in identifying patients with SCD and MCI that have a high risk of converting to dementia over a 5-year period. However, as the discriminant power of the method is of moderate degree, it should be added to other routine diagnostic methods like cognitive tests and other biomarkers.

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Statement of Ethics

All participants, or a family caregiver, were given oral and written information, and they consented to participation in writing in compliance with the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committees of the 3 countries, respectively.

Disclosure Statement

None of the authors have conflicts of interest.

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Author Contributions

K.E. contributed to the study design, did the analyses, evaluated the analyses, wrote the preliminary and last draft of the manuscript, and approved it. M.L.B., P.H., B.B.A., M.N., A.-R.Ø., L.-O.W., and J.S. took part in the study design, evaluated the analyses, gave input to the preliminary and last draft of the manuscript, and approved it. N.W.D. and T.E.G. gave input to the preliminary and last draft of the manuscript, and approved it.

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