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Prediction of longitudinal cognitive decline in normal elderly with subjective complaints using electrophysiological imaging

L.S. Prichep [a,b,*], E.R. John [a,b], S.H. Ferris [c], L. Rausch [a], Z. Fang [d], R. Cancro [b,e], C. Torossian [c], B. Reisberg [c]

[a] *Brain Research Laboratories, Department of Psychiatry, New York University School of Medicine, New York, NY 10016, USA*
[b] *Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA*
[c] *Silberstein Aging and Dementia Research Center, New York University School of Medicine, New York, NY, USA*
[d] *Department of Human Genetics, School of Medicine, University of California, LA, CA, USA*
[e] *Department of Psychiatry, New York University School of Medicine, New York, NY 10016, USA*

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Abstract

An extensive literature reports changes in quantitative electroencephalogram (QEEG) with aging and a relationship between magnitude of changes and degree of clinical deterioration in progressive dementia. Longitudinal studies have demonstrated QEEG differences between mild cognitively impaired (MCI) elderly who go on to decline and those who do not. This study focuses on normal elderly with subjective cognitive complaints to assess the utility of QEEG in predicting future decline within 7 years.

Forty-four normal elderly received extensive clinical, neurocognitive and QEEG examinations at baseline. All study subjects ($N = 44$) had only subjective complaints but no objective evidence of cognitive deficit (evaluated using the Global Deterioration Scale [GDS] score, GDS stage = 2) at baseline and were re-evaluated during 7–9 year follow-up. Baseline QEEGs of *Decliners* differed significantly ($p < 0.0001$, by MANOVA) from *Non-Decliners*, characterized by increases in theta power, slowing of mean frequency, and changes in covariance among regions, especially on the right hemisphere. Using logistic regression, an R^2 of 0.93 ($p < 0.001$) was obtained between baseline QEEG features and probability of future decline, with an overall predictive accuracy of 90%. These data indicate high sensitivity and specificity for baseline QEEG as a differential predictor of future cognitive state in normal, subjectively impaired elderly.

Keywords: Quantitative EEG; QEEG; Prediction of cognitive deterioration; Dementia; Longitudinal study; Brain imaging; Subjective cognitive impairment

1. Introduction

Numerous investigators have reported changes in the pattern of brain electrical activity (electroencephalogram, EEG) associated with aging and noted a relationship between specific changes in the EEG and clinical deterioration [4–9,14,18,26–28,39,42,46,50,51,55,58,59,61,63,65,68]. In a cross-sectional study, we reported a significant relationship between degree of cognitive impairment and magnitude of abnormalities in quantitative EEG (QEEG) [49]. Selected features of the QEEG have been demonstrated to significantly differentiate between patients with Alzheimer's disease (AD), vascular dementia and normal elderly controls [45].

In follow-up studies of patients with mild AD or mild cognitive impairment (MCI), QEEG features have been shown to be related to future decline. In a 1-year follow-up of 24 patients with mild AD [60], those with slow wave excess in the initial evaluation showed further EEG deterioration while those with normal EEGs did not. Jelic et al. [30] reported that baseline QEEG values of alpha and theta relative power and mean frequency from the left temporo-occipital region significantly separated MCI patients who go on to decline

* Corresponding author. Tel.: +1 212 263 6288/87; fax: +1 212 263 6457.
E-mail address: leslie.prichep@med.nyu.edu (L.S. Prichep).

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from those who do not, with a mean follow-up of 21 months. Huang et al. [28] followed a group of 31 MCI patients for 25 months and reported that those who progressed to AD had decreased alpha global field power (GFP) and anteriorization of the theta, alpha and beta sources, with the best predictor of decline being antero-posterior localization of alpha. In a 2-year follow-up of QEEG values in 15 patients with mild AD [25], from whom CSF acetylcholinesterase (AChE) values were available, 7 showed a further increase in theta with greater cognitive impairment. Although delta activity and AChE were correlated inversely ($r = -0.68$), there was no AChE difference between those with or without cognitive decline.

Golomb et al. [20,21] reported a relationship in normal elderly subjects between hippocampal atrophy and performance on tests of delayed memory, and further showed that the degree of atrophy significantly predicted longitudinal change on memory tests [22]. Longitudinal studies have demonstrated that abnormalities in the hippocampus [11,13,37], the entorhinal cortex [13,37], or the temporal neocortex [2,3,10] may predict conversion to dementia in MCI patients. Using magnetic resonance imaging (MRI) guided positron emission tomography (PET), de Leon et al. [12] studied evolution of dementia in normal elderly and reported that reduced glucose metabolism in the entorhinal cortex could predict future cognitive decline.

Most previous longitudinal studies were of elderly patients who had already met diagnostic criteria for MCI or mild dementia (generally AD). Since the earliest stages of Alzheimer's disease are hard to distinguish from changes due to "normal aging", it is important to study the decline from age expected normal values to understand the evolution of dementia and its correlation with neurophysiological abnormalities. This study examined the evidence that QEEG features associated with cognitive decline in the MCI and mild dementia populations (AD), especially increased theta activity, might be identifiable in the baseline evaluations of normal elderly subjectively impaired subjects who show decline at 7-year follow-up.

2. Methods

2.1. Subjects

Subjects were community residing elderly persons, 64–79 years of age, presenting with self-report of decline in cognitive functioning in response to referrals and public announcements from the New York University Silberstein Aging and Dementia Research Center (ADRC) for voluntary participation in a longitudinal study. Medical, neurological, psychiatric and neuropsychological evaluations were conducted by the ADRC to exclude patients with conditions apart from subjective cognitive impairments, which might interfere with or confound the assessment of cognitive functioning.

Criteria for exclusion in this study included: (a) past history of significant head trauma, seizures, mental retardation or neurological disorder; (b) any focal signs of significant neuropathology; (c) diagnosis of multi-infarct dementia based on a history of cerebral infarction or transient ischemic attacks including any patients with a modified Hachinski Ischemic score >4 [57]; (d) significant history of alcohol or drug abuse; (e) previous history of schizophrenia or major affective disorder, including any subjects with Hamilton Depression Scale (HAM-D) scores of $\geq$16 [24]; (f) cardiac, pulmonary, vascular, metabolic or hematologic conditions of sufficient severity to adversely affect cognition or functioning; (g) other physical impairment of sufficient severity to adversely affect cognition or functioning and (h) failure to discontinue any psychotropic or other centrally acting medication at least 2 weeks prior to the evaluation period. Written informed consent was obtained from all study subjects.

2.1.1. Staging for degree of cognitive decline

All subjects were assessed for the magnitude of cognitive decline at baseline at the ADRC, using the Global Deterioration Scale (GDS) for age-associated cognitive decline and primary degenerative dementia and those with a GDS score of 2 were considered as potential study subjects. Details of this widely used procedure are given elsewhere [52,53]. Briefly, subjects at GDS stage 1 are free of subjective complaints or objective evidence of cognitive impairment. Subjects at GDS stage 2 have subjective complaints in the absence of objectively manifest deficits. Subjects at GDS stage 3 have mildly manifest deficits consistent with a diagnosis of MCI [15]. Subjects at GDS stage 4 or greater meet DSM IV criteria for dementia of progressively increasing severity (maximum, stage 7). The validity and reliability of this staging procedure have been reviewed elsewhere [54].

2.1.2. Study population

During the duration of subject enrolment (from 1980 to 1997), 118 normal elderly with a baseline GDS stage of 2 were referred to the Brain Research Laboratories for EEG testing, of which 44 subjects completed the longitudinal follow-up staging at the 7-year time point and formed the study population (see Table 1 below). There were no significant differences in demographics for age ($p < 0.190$) or gender ($p < 0.112$) distributions, between the longitudinally followed subset of all subjects and the general referral population, confirming the followed subset them to be representative of the GDS = 2 normal elderly population referred. The 74 subjects referred for evaluation, but lost to follow-up were mainly those who moved from the area, died, refused follow-up or whom we were unable to locate. The median length of time between staging evaluations and subsequent EEG evaluations was 1.7 months with no significant differences in this time interval between the outcome groups ($p < 0.5433$).

The 44 study subjects consisted of 22 females and 22 males with a mean age of 72.0 years (64.6–79.8 years). At baseline,

Table 1
Demographic and diagnostic data from baseline evaluations of the outcome groups

Demographics	Change in GDS stage	
	Non-decliners	Decliners
Number of subjects	17	27
Mean age (year)	70.0 (4.1)	73.5 (4.9)
Age range (year)	64.7–77.8	64.6–79.8
Education level (year)	15.9 (2.4)	14.8 (3.3)
n Female	9	13
n Male	8	14
Initial diagnosis		
Normal [NL]	13	23
NL with CVD[a]	4	4
GDS[b] at follow-up	2	3–5
MMSE[c] baseline[d]	29.7 (0.7)	28.4 (1.8)
Years to maximum change/stability[e]	8.9 (1.8)	5.2 (1.4)

When mean values are shown, the standard deviations (S.D.) are given in parentheses. All subjects were followed for ≥7 years. For the decliners the time of the most significant change in GDS during the 7-year interval was used. There were no significant differences between demographic or diagnostic variables between the two outcome groups.

[a] CVD, cerebrovascular disease.

[b] GDS, Global Deterioration Scale.

[c] MMSE, Mini Mental Status Examination.

[d] Only available for subjects whose baselines were obtained from 1983 on, for a total of 9 non-decliners and 17 decliners.

[e] Follow-up interval was longest for the non-decliner group to validate the lack of conversion throughout the longest longitudinal interval available.

36 (82%) of the subjects had a diagnosis of normal aging (NL) and 8 (18%) had a diagnosis of normal with cerebrovascular disease (NL-CVD). Normals with cerebrovascular disease were those with cognition and functioning found to be within normal limits (GDS stage = 2) with evidence of cerebrovascular disease from medical and/or neurological evaluations, but with Hachinski Ischemia scores <4.

2.1.3. Follow-up and outcome groups

The GDS status of each subject was re-evaluated at varied points throughout the 7-year period following their baseline evaluation. For the purpose of statistical comparisons, subjects were divided into two *outcome groups* based upon the GDS status during follow-up. The *Non-Decliners* ($n = 17$) included those who remained at GDS stage 2 after at least 7 years. In some of these cases, no change was documented for more than 7 years, resulting in a longer follow-up interval, demonstrating the longest interval of stability observed in this group. The *Decliners* ($n = 27$) included both those who: (a) declined mildly to MCI ($n = 20$, GDS = 3) at some point, but showed no further decline during the 7-year follow-up period or (b) received a diagnosis of dementia ($n = 7$, GDS ≥ 4) during the 7-year follow-up period. For those subjects who showed decline, the maximal deterioration within the 7-year period was used for the analyses. In some cases, the maximum decline occurred in <7 years. All subjects who declined to dementia were diagnosed using the NINCDS-ADRDA criteria as being AD, or in one case, vascular dementia [44]. The range of the follow-up period of the study was 5.2–8.9 years, as shown in Table 1.

2.2. Neuropsychological and mental status measures

In addition to GDS staging, a neuropsychological evaluation was used to assess four cognitive domains, using the indicated instruments:

(a) *Memory*: Three subtests of the Guild Memory Scale [19], including: (a) *paragraph recall* of orally presented meaningful material, initial (PARI) and delayed (PARD); (b) *paired associate recall* of associations between pairs of familiar words, initial (PRDI) and delayed (PRDD) and (c) *designs recall* (DESN) of abstract shapes; and the digit recall subtests of the Wechsler Intelligence Scale Revised (WAIS-R, [67]), forward (WAIS-R DIG-F) and backward (WAIS-R DIG-B).
(b) *Perceptual motor skill*: Digit symbol substitution subtest (DSST) of the WAIS-R.
(c) *Language function*: Vocabulary subtest (WAIS-R-V) of the WAIS-R.
(d) *Mental status assessment*: Mini-Mental State Exam (MMSE) [16] and/or the Mental Status Questionnaire (MSQ) [36].

2.3. EEG data acquisition

At the initial visit, subjects were seated comfortably in a light attenuated room while 20 min of eyes closed resting EEG data were collected from the 19 monopolar electrode sites of the International 10/20 System, using silver/silver chloride electrodes referenced to linked earlobes. Data acquisition was performed on either a Brain State Analyzer (Cordis Corporation) or a Spectrum 32 (Cadwell Laboratories). A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points), with a 60 Hz notch filter. Data were sampled at a rate of 200 Hz with 12 bit resolution.

2.4. EEG data analysis

The neurometric QEEG method was used [34]. Quantitative features were extracted, log transformed to obtain normal (Gaussian) distributions [17,31], age-regressed and *Z*-transformed relative to age appropriate population norms. These population norms have been repeatedly confirmed to be independent of ethnic or cultural bias [29]. It is noted that the normative population was evaluated in the same manner as subjects in this study, and that the age range of the study sample was well represented in the construction of the normative equations. *Z*-values or standard scores for these features (proportional to probabilities) were used for all analyses. This method allows the statistical assessment of the

significance of departure from age expected normal values, thus taking into account (correcting for) the normal effects of aging. The importance of each of these steps in enhancing the clinical utility of electrophysiological data has been discussed in detail elsewhere [32,34,47,48].

Artifact removal was performed by visual inspection of the raw EEG data, augmented by a computerized artifact detection algorithm (amplitude driven). One to 2 min of artifact-free EEG data (24–48, 2.5 s epochs) were subjected to power spectral analysis using Fast Fourier Transform (FFT). For each of the 19 monopolar derivations, the absolute and relative (%) powers and mean frequencies were computed for the delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25 Hz) frequency bands, as well as the total spectral power. Inter- and intra-hemispheric measures of coherence and symmetry between regions were also computed for the four frequency bands and total power. Topographic images of group average QEEG *Z*-scores were constructed to facilitate review of these univariate features for each outcome group.

In addition to the univariate features, two types of composite features were computed that represent multivariate abnormalities of two main types: (i) relations among a set of spectral features within a specific topographic location (e.g. left frontopolar absolute power) or (ii) relations of a specific spectral feature among a set of topographic regions (e.g. anterior alpha asymmetry). These features are Mahalanobis distances which take into account the covariance matrix among multiple features. They provide conservative quantification of the combinations of measures, which reflect relationships among neurophysiological processes and interactions among brain regions and serve as an important means of data reduction. Validations and replications of the normative data have been published for the multivariate as well as univariate measures [33].

2.5. Statistical analyses

2.5.1. Comparison between non-decliners and decliners

In order to statistically assess the significant differences between the outcome groups, the following methods were used:

(a) One-way ANOVAs by outcome group were computed for each of the neuropsychological variables.
(b) A multivariate analysis of variance (MANOVA) by outcome group was computed for a selected subset of QEEG features. To facilitate data reduction of the large number of features extracted from each QEEG analysis prior to entry to the MANOVA, one-way ANOVAs by group were computed for each EEG frequency band and *F*-values from these ANOVAs were color coded and displayed as topographic maps. To adjust for the large number of comparisons made, only findings significant at the $p < 0.01$ level were considered for further analyses. Multivariate QEEG features best reflecting the bands and regions of ANOVA significances were selected for entry to the MANOVA analysis. Further, the most highly significant univariates within each measure set were also entered into the MANOVA.

2.5.2. Prediction of degree of decline using logistic regression

A logistic regression procedure (SAS/STAT Proc Logistic) was used to determine the degree to which a finer distinction of longitudinal outcome could be predicted from baseline neurometric QEEG features. That is, *Decliners* were divided into two sub-groups: those who declined to a diagnosis of MCI (*Mild Decliners*, $N = 20$, GDS = 3) and those who converted to dementia, in all cases a diagnosis of dementia (*Converters*, $N = 7$, GDS ≥ 4, [6 of the 7 to GDS = 4 and 1 of 7 to GDS = 6]). *Non-Decliners* ($N = 17$, GDS = 2) remained as before. The logistic regression procedure fits a common slope cumulative model, which is a parallel lines regression model, based on the cumulative probabilities of the response categories rather than on their individual probabilities.

As above, preliminary analyses were necessary to reduce the measure set and select a subset of variables for entry to the logistic regression. Several methods were implemented to achieve this goal, including: (a) multivariate stepwise discriminant analysis (SAS PROC DISCRIM) between the three GDS outcome groups. Since this approach was used to prune the measure set and not to achieve optimized separation, a moderate significance level was sought and results are not presented herein; (b) results of three way ANOVAs described above and (c) heuristic selection also considered electrophysiological results previously reported in the scientific literature as reviewed above.

3. Results

3.1. Outcome groups

Table 1 shows the baseline demographic information for the two outcome groups (*Non-Decliners and Decliners*). No significant differences were found for age, gender, education or initial diagnosis between the two outcome groups.

3.2. Neuropsychological evaluations

ANOVAs were computed for any neuropsychological measure in which the mean values had a linear progression with outcome, since only such measures would be of potential predictive utility. The means, standard deviations and significance of the differences between outcome groups for baseline values of the neuropsychological measures are shown in Table 2. Significant outcome group effects were found for baseline scores for DSST [$F(1,42) = 5.11$, $p < 0.03$], WAIS-R DIG-F [$F(1,42) = 7.83$, $p < 0.01$] and WAIS-R DIG-B [$F(1,42) = 5.96$, $p < 0.02$]. As can be seen in Table 2,

Table 2
Neuropsychological baseline measures (mean and in parentheses, standard deviations, for clinical outcome groups and the significance of differences (ANOVA, *F* values and probability) between the groups

Baseline measure[a]	Outcome group		*F*-value	Probability
	Non-decliners ($n = 17$) × (S.D.)	Decliners ($n = 27$) × (S.D.)		
MSQ	1.4 (3.3)	1.4 (3.2)	0.01	0.93
PAR I	9.1 (2.2)	8.5 (3.3)	0.44	0.51
PAR D	10.9 (3.2)	10.54 (4.2)	0.10	0.75
PRD I	4.6 (1.9)	4.7 (2.3)	0.03	0.86
PRD D	5.5 (2.6)	4.4 (2.6)	1.91	0.17
DESN[b]	6.2 (2.2)	5.4 (1.7)	1.71	0.20
WAIS-R DSST	54.4 (8.6)	45.0 (15.5)	5.11	0.03
WAIS-R-V	70.5 (6.5)	66.6 (13.6)	1.22	0.28
WAIS-R DIG-F	7.9 (1.1)	6.7 (1.4)	7.83	0.01
WAIS-R DIG-B	6.1 (1.4)	5.1 (1.3)	5.96	0.02

[a] MSQ, Mental Status Questionnaire; PAR I, paragraph initial recall; PAR D, paragraph delayed recall; PRD I, paired associate initial recall; PRD D, paired associate delayed recall; DESN, designs recall; DSST, digit symbol substitution test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R); WAIS-R V, vocabulary test of the WAIS-R; WAIS-R DIG-F, digit span recall forward of the WAIS-R; WAIS-R DIG-B, digit span recall backward of the WAIS-R.
[b] One subject from the non-decline group was missing this test, therefore the *N* for this test was 43.

although significant, there was a high degree of overlap between groups in the distributions of these measures.

3.3. Quantitative EEGs

3.3.1. QEEG brain images

Fig. 1 shows baseline group average *Z*-score topographic images from the two outcome groups, for absolute power (top panel), relative power (middle panel) and mean frequency (bottom panel) in the delta, theta, alpha and beta frequency bands (successive columns). The color scale of each image is in standard deviation units (converted to probability) relative to the distribution of age expected normal values. The color scale takes into consideration the fact that to estimate the significance of *Z*-scores for group average data, the mean *Z*-score should be multiplied by the square root of the number of patients in the group.

Although all patients were GDS 2's at the time of this baseline evaluation, clear QEEG differences were already evident between the two outcome groups. The *Non-Decliners* had absolute power, relative power and mean frequency values within normal limits for their age, whereas widespread excess of absolute and relative power in the theta band (right hemisphere greater than left) and diffusely increased theta and decreased alpha mean frequency were seen in the *Decliners*. While not shown in the figure, few significant differences were seen between outcome groups for measures of power symmetry, gradients or synchrony, within or between hemispheres, with the exception of inter-hemispheric delta power asymmetry in the delta band (with significant excess of power on the right).

Fig. 2 contains topographic maps of *F*-values from the ANOVAs for the significance of outcome group differences for absolute power (top row), relative power (middle row) and mean frequency (bottom row) in the delta, theta, alpha and beta frequency bands (successive columns). It is emphasized that these maps are shown only for purposes of summary and data compression. Since an *F*-value of 7.27 has a probability of $p < 01$ (d.f. = 1.42), this figure displays extremely high significance values. The ANOVAs showed the most significant differences ($p < 0.01$) between the groups for: (a) theta absolute power, especially in the frontal, midline and right posterior regions; (b) theta and beta relative power, especially in the central, anterior temporal and lateral frontal regions and (c) for theta and alpha mean frequency, especially in posterior regions and for theta in the left lateral regions.

3.3.2. Outcome group effects

Highly significant outcome group effects were found [MANOVA, $F(12,31) = 5.08$, $p < 0.0001$] using 13 baseline QEEG features. The most significant features included: (a) relative theta power in left lateral regions (F7, T3 and T5);

Table 3
Mean probability of prediction and percent correct classification of predicted group membership based on logistic regression from selected QEEG baseline variables

Group	*N*	Mean probability of prediction			Correct classification[a] (%)
		Non-decliners GDS 2 at FU	Mild-decliners GDS 3 at FU	Converters GDS ≥ 4 at FU	
Non-decliners	17	0.92	0.08	0.00	94.1
Mild-decliners	20	0.07	0.87	0.06	90.0
Converters	7	0.00	0.17	0.83	85.7

[a] Cut-off probability ≥0.50 used for correct classification.

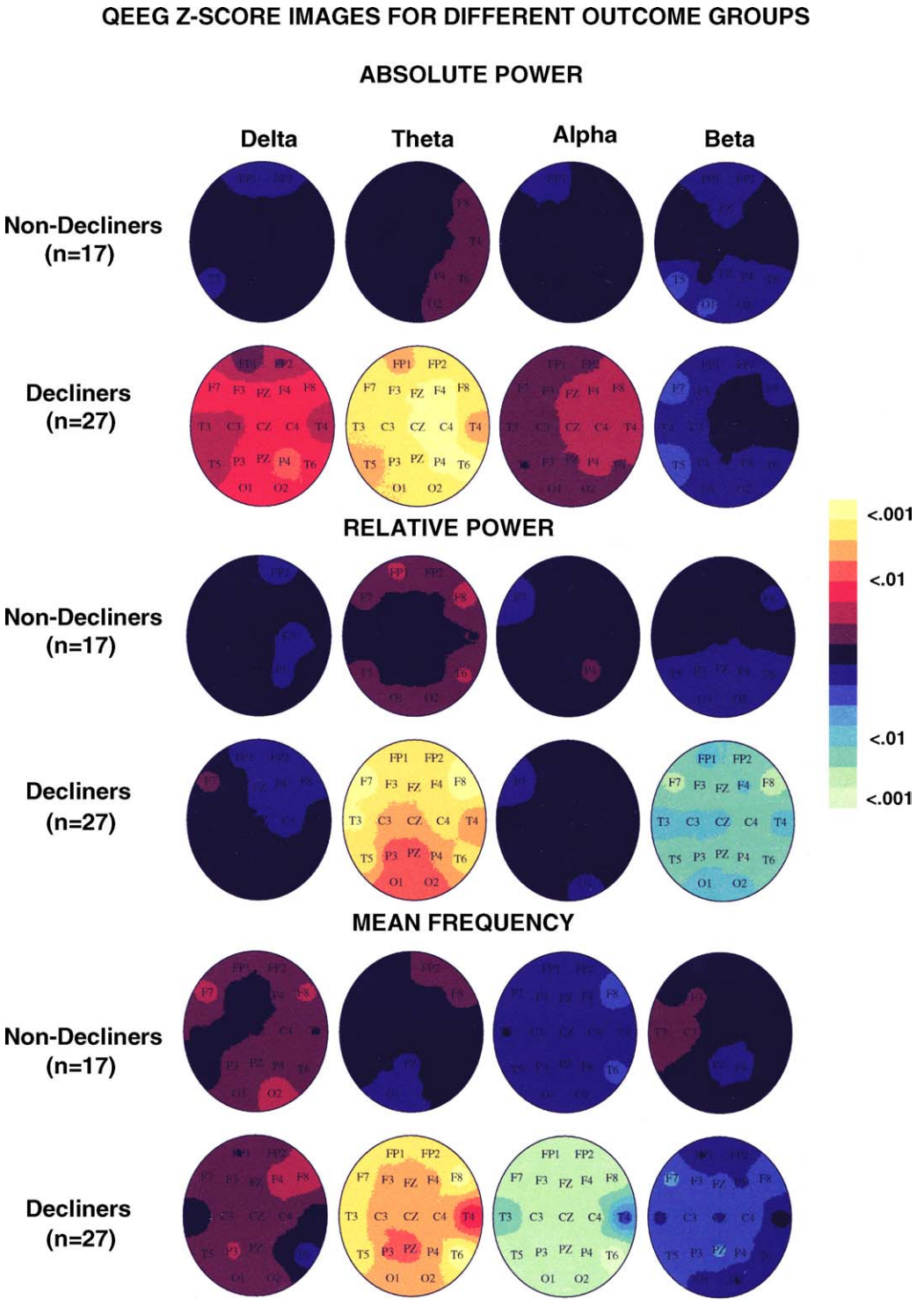

Fig. 1. Baseline group average *Z*-score topographic images for absolute power (top panel) and relative power (middle panel) and mean frequency (bottom panel), in the delta, theta, alpha and beta frequency bands (successive columns) for the three outcome groups: non-decliners ($n = 17$, first row) and decliners ($n = 27$, second row) of each panel. The color scale of each *Z* image is in standard deviation units. To estimate the significance of any regional *Z*-score for this group average data, the *Z*-score should be multiplied by the square root of the number of patients in the group. In this figure, the extremes of the scale are at the $p < 0.001$ for the smallest group. Marks (<) is placed on the *F* scale, indicating the $p = 0.001$ and 0.01 significance levels at each end of the scale (excess, red to yellow, and deficit, dark blue to light green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

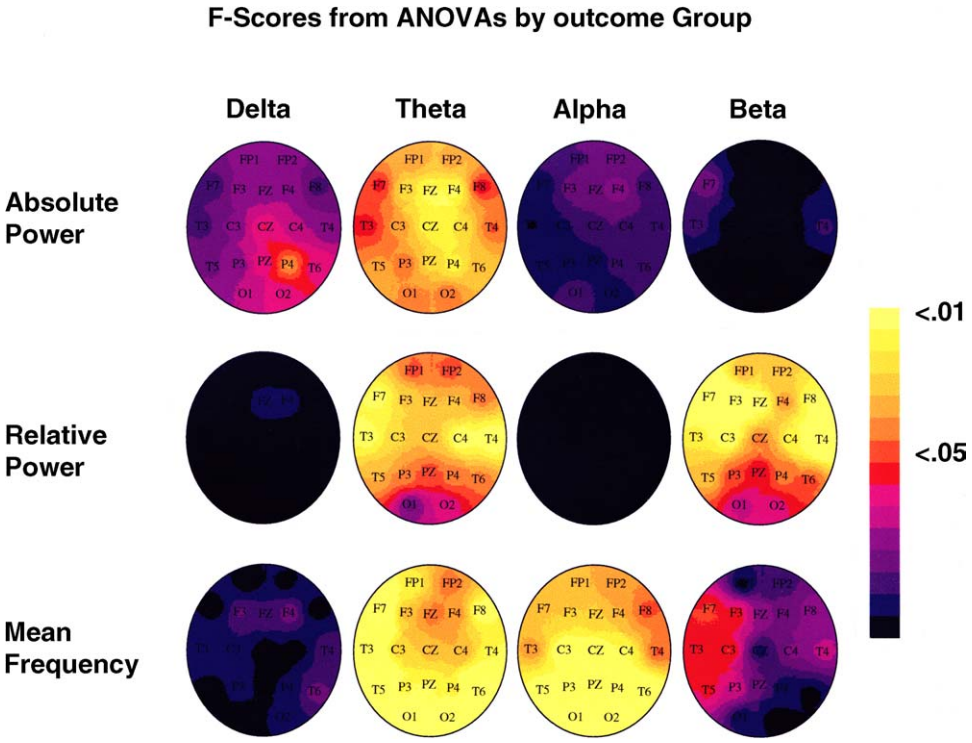

Fig. 2. The topographic distribution of *F*-values from the ANOVA's for the significance of baseline differences between the two outcome groups for absolute power (top row), relative power (middle row) and mean frequency (bottom row), in the delta, theta, alpha and beta frequency bands (successive columns). An *F*-value of 7.3 has a probability of less than or equal to $p < 0.01$ (d.f. = 1.42). Marks (<) are placed on the *F*-scale, indicating the $p = 0.01$ and 0.05 significance levels.

(b) coherence across all frequency bands between the right central and posterior regions (C4 and P4); (c) mean frequency of theta in F7; (d) mean frequency of the total spectrum in T4 and (e) absolute power in theta in the right medial (FP2, F4, C4, P4 and O2) and posterior temporal (T6) regions.

3.3.3. Logistic regression

Table 3 shows the results of the logistic regression using selected QEEG baseline features. The first three columns of this table show the mean probability of prediction and the last column the accuracy of the prediction, for each group.

The overall prediction accuracy was 90%, with an R^2 of 0.93, $p < 0.0001$, based on 9 QEEG baseline variables. Variables with the highest significance in the prediction equation included: mean frequency of the total spectrum on right central region (C4); mean frequency in the delta band on the left bipolar temporal region (T3T5) and parietal occipital region (P3O1); absolute power across all frequency bands diffusely on the right hemisphere and more specifically on the right dorsolateral frontal region (F8); and absolute power in the theta frequency band across the right anterior regions (FP2, F4 and F8).

Sensitivity was 88.9% and specificity 84.3% for the correct prediction of any deterioration (including decline to MCI, as well as conversion to dementia). Considering only those who in fact converted to dementia (GDS ≥ 4), the sensitivity was 96.3% and the specificity was 94.1%. Considering only those who decline to MCI, the sensitivity was 95% and specificity was 94.1%. The few misclassifications of the regression are of interest to note: (a) there were two misclassification of *Mild Decliners*, one was predicted to belong with the *Converters* and the other with *Non-Decliners* and (b) one subject who converted to dementia was predicted to belong with the *Mild Decliners*. None of the misclassifications were more than one step from the classification of the clinical follow-up, indicating that the function had high specificity.

To explore the utility of a multidimensional regression, ANOVAs of the neuropsychological scores were repeated for the three outcome groups. Three neuropsychological measures were significant in both the two and three way ANOVAs. The significances of these variables in the three way ANOVAs were: DSST [$F(2,41) = 4.11$, $p < 0.02$], WAIS-R DIG-F [$F(2,41) = 4.13$, $p < 0.02$] and WAIS-R DIG-B [$F(2,41) = 3.81$, $p < 0.02$]. Table 2 above gives the probabilities for the two-way ANOVAs. These three neuropsychological variables were first entered into a logistic regression in order to evaluate their predictive accuracy alone. The R^2 for this logistic regression was 0.26, suggesting that the psychometric data alone was not predictive of subsequent decline. However, when these variables were added to the QEEG logistic regression, the overall predictive accuracy of this combined logistic regression was increased to an R^2 of 0.97, $p < 0.0001$.

4. Discussion

While a multitude of studies have demonstrated a significant relationship between cognitive decline and abnormalities in brain electrical activity, especially slow wave excess, few studies have investigated the utility of the presence of such abnormalities for predicting future deterioration. Further, the focus of most of these prediction studies was on MCI patients who were already manifesting impairments clinically. In the current study, the focus was on the predictive utility of QEEG from baseline studies of normal elderly subjects with only subjective complaints of cognitive decline (GDS = 2). High sensitivity and specificity were demonstrated for baseline QEEG evaluations as predictors of future cognitive decline to MCI and/or conversion to dementia over a 7-year period.

Highly significant outcome group effects ($p < 0.0001$) were found for QEEG baseline features comparing *Non-Decliners* to *Decliners*. Using logistic regression to predict non-decline, decline or conversion, overall prediction accuracy was 90%, with an R^2 of 0.93 ($p < 0.0001$). Multivariate composite features which quantify the covariance among multiple univariate QEEG measures contributed most to the MANOVA, and to the high predictive accuracy of the logistic regression. Such features describe relationships among neurophysiological processes within, and interactions among, brain regions. Of particular importance were absolute power across all frequency bands within the right hemisphere and on the right dorsolateral frontal cortex; absolute power in the theta frequency band across the right anterior and medial regions; mean frequency across all bands in the right hemisphere; relative power in the theta frequency band across the left lateral regions and intra-hemispheric coherence between right central and parietal regions. The extent of the regions involved and the QEEG measures contributing to the prediction accuracy suggest the diffuse nature of MCI and AD.

Increase in theta and changes in the overall power of the QEEG reflect transactions between the hippocampus, the septal nuclei, the reticular formation, the thalamus and the neocortex [40,41,43,64]. Significant negative correlations were found between frontal theta power and hippocampal volume in a population of normal elderly, mild cognitive impairment and mild dementia [23]. In studies of dementia patients, Rodriguez et al. [56] found significant negative correlations between theta power and perfusion level in the right hippocampus, and Mattia et al. [42] reported similar widespread findings, including anterior and central regions, suggesting that hypoperfusion may be present at baseline in the elderly with only subjective memory complaints who go on to decline over time. In one of the few published studies of predictability of subsequent decline in normal elderly, de Leon et al. [12] used baseline MRI-guided PET scans to study evolution of dementia and reported that reduced glucose metabolism in the entorhinal cortex could predict future cognitive decline.

Changes in coherence or synchronization between brain regions have been shown to relate to the degree of dementia [5] and to differentiate between patients with AD and those with MCI or only subjective memory complaints [63]. The present findings suggest that when such changes in the relationships between regions appear in the normal elderly, they are predictive of later cognitive decline.

Although all outcome groups had neuropsychological function within normal limits at baseline, with clearly overlapping distributions, those who showed deterioration at follow-up generally had lower mean scores at baseline than those who did not decline. Significant differences at baseline between outcome groups were found for the digit symbol substitution test (DSST) and the digit span forward (DIG-F) and backward (DIG-B) tests. Such tests are considered to reflect information processing speed and visual motor coordination (DSST) and to tap attentional/concentration aspects of memory (DIG-F and DIG-B), rather than those dependent upon storage and retrieval, such as the paragraph delayed recall (PAR D), which has been reported to be predictive of future decline in elderly populations including patients with MCI diagnoses [38]. Although the significant neurocognitive measures did not show significant predictive power (R^2 of 0.26), probably due to the greatly overlapping distributions of these measures between the groups, when they were added to the selected QEEG variables, the overall predictive accuracy was increased to an R^2 of 0.97 ($p < 0.0001$), with almost perfect classification accuracy. These results are suggestive, but need to be considered with caution, as the N was not sufficient to divide the group into a test and train split-half, and therefore await prospective independent replication.

Also of interest are findings from the 8 NL-CVD subjects (i.e. those with either a history of cerebrovascular disease, but with Hachinski Ischemic scores <4 and normal behavioral and cognitive function with only subjective complaints of cognitive impairment at baseline). These subjects were not differentially distributed in the outcome groups, suggesting that the QEEG baseline indicators of future cognitive decline were independent of history of cerebrovascular disease.

Since this study did not obtain repeat QEEG evaluations at follow-up, we are unable to determine whether the abnormal brain activity seen in the initial evaluation reflects the earliest stage of a process evolving further during progressive decline, or is a trait marker predictive of further brain dysfunction and eventual decline. The extent of the regions involved, and the measures found to be significantly abnormal in the baseline evaluations, suggest that QEEG evaluations may be a sensitive indicator of the earliest states of structural abnormalities, detecting them earlier than the conventional imaging tools.

A meta analysis on studies of the prevalence of memory complaints in the elderly and their relationship to decline to dementia, reports that a substantial proportion of the elderly have subjective complaints of cognitive impairment and that data suggests an association between such subjective com-

plaints and decline to dementia [35]. It is increasingly emphasized that interventions or preventive strategies related to treatment of dementia could have the most impact if applied at the earliest possible time [1,62,66]. Further, preventive treatment studies would benefit greatly by the identification of at-risk normal elderly populations, thereby limiting otherwise prohibitively large sample sizes and study durations. Thus, early identification of those most likely to decline to dementia is of paramount importance.

This study demonstrates the potential clinical utility of QEEG, which has high predictive validity in the initial evaluation of normal elderly presenting with subjective complaints of cognitive decline, prior to objective evidence of impairments or diagnostic signs of MCI or AD. A prospective replication with an independent sample is necessary for the demonstration of robustness of this approach; such a study is currently in the follow-up phase. Future studies including more general community subject populations and other types of dementia are also necessary to evaluate the potential clinical utility of the QEEG methodology as a tool for aiding early identification of those targeted for prevention trials. When replicated, these results suggest that QEEG represents an objective, cost-effective, culture-fair, age-regressed, noninvasive evaluation method, highly sensitive to the probability of future decline in the normal elderly population.

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