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Addition of EEG improves accuracy of a logistic model that uses neuropsychological and cardiovascular factors to identify dementia and MCI

Steven Michael Snyder [a,b,*], James Richard Hall [a], Sonya Lynn Cornwell [a], James David Falk [b]

[a] Department of Psychiatry and Neuroscience, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas, 76107, USA
[b] Lexicor Medical Technology, Augusta, Georgia, 30901, USA

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ABSTRACT

To investigate whether addition of EEG would improve accuracy of a logistic model that uses neuropsychological assessment and cardiovascular history to identify dementia and mild cognitive impairment (MCI) as a single group, we collected data and constructed logistic models from a sample of 78 normal adults and 33 patients (aged 50–85 years). To determine accuracy, we compared logistic regression results to a geriatrician's diagnosis of MCI or dementia that included Alzheimer's disease, vascular dementia or mixed dementia. We found that the addition of EEG (non-linear complexity) to a logistic model that included both neuropsychological assessment (ADAS-Cog) and cardiovascular history increased overall accuracy from 80% to 92%. The logistic model identified dementia and MCI as a single group comprised of the following subgroups (with accuracies): Alzheimer's disease (92%; 12/13), vascular dementia (73%; 8/11), mixed dementia (100%; 4/4), and mild cognitive impairment (80%; 4/5). Whereas the analysis is limited by small sample sizes and mixing of diverse pathologies, the findings do provide support that the subgroups may share changes in neuropsychological, cardiovascular, and electroencephalographic factors (specifically ADAS-Cog total score, cardiovascular history, and EEG complexity). Taken together, the study results provide support that EEG might complement the clinician's evaluation of dementia and MCI.

1. Introduction

The prevalence of dementia in our aging population presents a need for reliable assessment methods. Commonly recommended methods include neuropsychological testing, CSF 14-3-3 protein analysis, and structural neuroimaging using magnetic resonance imaging (MRI) or computed tomography (CT) (Knopman et al., 2001; Waldemar et al., 2007). Promising methods under research include genetic testing, cardiovascular risk factors, electroencephalography (EEG), and diagnostic imaging using positron emission tomography (PET) or single photon emission computed tomography (SPECT) (McKann et al., 1984; Knopman et al., 2001; Rosendorff et al., 2007; Waldemar et al., 2007).

Given a variety of assessment methods, clinical application can be assisted by an understanding not only of performance of the individual methods, but also of the cumulative performance when integrating the methods. For instance, the addition of neuroimaging to clinical workup increased positive prediction of dementia from 80% to 95% (Aichner et al., 1996). Inclusion of neuropsychological testing with MRI in the diagnostic work-up improved reliability of differential diagnosis of dementia (Hentschel et al., 2005).

With that strategy in mind, the current study will focus on the integration of neuropsychological testing, cardiovascular risk factors, and EEG. Neuropsychological testing is currently recommended as a basic tool in the determination of cognitive decline and dementia (AGS, 2003). Accuracy results for neuropsychological testing include 60–98% sensitivity and 88–98% specificity for neurodegenerative and vascular dementias (55 dementia; 45 controls) (Hentschel et al., 2005). Neuropsychological testing has predicted dementia progression with 53–80% sensitivity and 67–99% specificity (by a review of multiple studies) (Jacova et al., 2007).

Recent evidence supports the importance of the cardiovascular system in development of not only vascular dementia (VAD), but also Alzheimer's disease (AD) and mild cognitive impairment (MCI). All of the main risk factors for AD and MCI are also known to be risk factors for cardiovascular disease (Meyer et al., 2000a; de la Torre, 2004; Nash and Fillit, 2006). These risk factors include hypertension, diabetes, cholesterol, atherosclerosis, smoking, atrial fibrillation, APOE genotype, homocysteine concentration, dietary saturated fats, antioxidants, alcohol consumption, lack of physical activity, and abnormalities in hemostatic and thrombotic factors (Breteler, 2000; Rosendorff et al., 2007).

EEG changes have been associated with dementia in numerous studies leading to many prospects for dementia identification (Soininen et al., 1982; John et al., 1988; Leuchter et al., 1993; Jeong, 2004). For instance, EEG activity analyses have identified AD presence with 66–74% sensitivity and 82–94% specificity (35 AD; 35 controls) and 98% sensitivity and 100% specificity (50 AD; 46 controls) (Mody et al., 1991; Bennys et al., 2001). Hazard ratio analyses applied to EEG

* Corresponding author. 2840 Wilderness Place, Suite E, Boulder, Colorado, 80301, USA. Tel.: +1 706 447 1074; fax: +1 303 443 0591.
E-mail address: ssnyder@hsc.unt.edu (S.M. Snyder).

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mean frequency or beta activity have been used to predict progression of AD (Lopez et al., 1997; Claus et al., 1998). Changes in EEG coherence and amplitude have been correlated with degree of dementia; $r = 0.87$ (Brunovsky et al., 2003).

Studies have supported that EEG and neuropsychological assessment may provide complementary information in identifying AD (Ihl et al., 2000). EEG integrated with neuropsychological testing differentiated frontotemporal lobe dementia and AD with 93% accuracy (36 AD; 44 controls). Furthermore, an EEG classification model adjusted by neuropsychological testing detected MCI with 85% accuracy (27 MCI; 16 controls) (Jelic et al., 2000).

To our knowledge no previous studies have examined the integration of EEG with neuropsychological testing and cardiovascular history in identifying dementia and MCI. We speculated that application of such a classification model to a variety of dementia and MCI subgroups would provide insights into associations between the subgroups. Therefore we investigated whether addition of EEG would improve accuracy of a logistic regression model that included both neuropsychological assessment and cardiovascular history to identify dementia subtypes and MCI as a single group. An improvement in accuracy may provide insights as to whether the different subgroups may share changes in cardiovascular history, neuropsychological testing and EEG. Because cardiovascular history and neuropsychological testing were incorporated to an extent in the reference standard, an improvement in accuracy would provide support that EEG in particular may offer additional information that could be of use to the clinician in their identification of dementia and MCI. We determined accuracy in a sample aged 50–85 years that comprised normal adults and patients with MCI, AD, VAD, or mixed dementia.

2. Methods

2.1. Study subjects

The study was approved by institutional review board (IRB) at the University of North Texas Health Science Center (UNTHSC). Appropriate protection of human subjects was maintained through the UNTHSC Office of Protection of Human Subjects. Informed consent was obtained from all subjects.

Participants were community-dwelling individuals 50–85 years of age who receive dementia and geriatric healthcare from the UNTHSC Geriatric Medicine Clinic (over 600 new patient evaluations/year; approximately 60% cognitively intact and 40% MCI or dementia). The sample comprised patients who responded to recruitment requests during the course of regular checkups from October 26th, 2004 to March 7th, 2006.

The sample of 111 individuals comprised 78 normal adults and 33 patients with MCI or mild to severe dementia. Dementia subtypes comprised 15.2% (5/33) MCI, 39.4% (13/33) AD, 33.3% (11/33) VAD, and 12.1% (4/33) mixed dementia (AD and VAD). Severity of dementia ranged from mild to severe (with MCI included) per total score of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): 1–10 (15.2%; 5/33), 11–20 (36.4%; 12/33), 21–30 (21.2%; 7/33), and >30 (27.3%; 9/33). Age ranges in years for dementia were 19.2% <65 years, 26.9% 65–70, 24.4% 70–75, 17.9% 75–80, and 11.5% >80 and for normal adults 15.2% 65–70 years, 24.2% 70–75, 24.2% 75–80, and 36.4% >80.

The demographics of the total sample comprised: 1) 63.1% women, 36.9% men; 2) 36.9% aged 55–70 years, 63.1% aged 71–85 years; 3) 7.2% African-American, 0.9% Asian-American, 84.7% Caucasian, 4.5% Hispanic, 2.7% other race; 4) 59.5% married, 3.6% single, 13.5% divorced, 23.4% widowed; 5) 57.7% overweight per body mass index; 6) 7.2% less than high school education, 45.9% high school education, 22.5% Bachelors degree, 12.6% Masters degree, 6.3% Ph.D. An education greater than high school was true of 45.2% of normal subjects and 40.6% of dementia patients. Further sample characteristics as well as ADAS-Cog scores and EEG results are presented in Table 1 with between-group analyses (dementia vs. normal; one-way ANOVA; two-tailed; age as covariate with EEG if significant). Demographic and medical factors are presented in Table 2 with risk analyses (dementia vs. normal; odds ratio).

2.2. Inclusion/exclusion criteria

Inclusion/exclusion was determined using the study's dementia reference standard, a previous diagnosis in patient records from UNTHSC Geriatric Medicine Clinic. Inclusion in the normal group required absence of neurological or psychiatric disorders, epilepsy, or recent injury. Inclusion in the dementia group required a previous diagnosis of MCI, AD, VAD, or mixed dementia. Each diagnostic evaluation had been determined by one of five board-certified geriatric physicians with assistance from two geriatric nurse practitioners and two geriatric social workers. Evaluations had included the following information: 1) medical history, 2) physical examination, 3) blood and/or urine analyses, 4) neuroimaging (MRI or CT), 5) neuropsychological assessment, 6) TSH, B12, and folate analyses, and 7) VDRL analysis (when appropriate). AD evaluations followed NINCDS-ADRDA criteria (McKann et al., 1984).

Other requirements for inclusion were: 1) subjects having good health and living in an independent setting, 2) written consent by subject (and spouse when appropriate), and 3) no recent history of drug/alcohol abuse. Prior to EEG recordings, subjects needed to be free of psychotropic medications (≥2 weeks) and medications known to affect central nervous system (≥1 week).

2.3. Procedure/instruments

To investigate whether addition of EEG would improve accuracy of a logistic model that used neuropsychological assessment and cardiovascular history to identify dementia and MCI as a single group, we collected data and constructed logistic models from a sample of normal adults and patients with MCI or dementia. For neuropsychological assessment, ADAS-Cog was collected at UNTHSC Geriatric Psychology Center by

Table 1
Analysis of between-group differences (normal vs. dementia).

	Normal	Dementia
Age	70.4 (7.8)	76.6 (5.7)[b]
Body mass index	27.3 (6.4)	26.0 (4.3)
Number of surgeries	4.4 (3.4)	4.4 (3.1)
Years since last surgery	12.1 (18.0)	12.3 (14.9)
Self rating: depression (0–10 depressed)	1.95 (2.17)	2.63 (2.56)
Self rating: anxiety (0–10 anxious)	2.72 (2.05)	3.70 (3.21)
ADAS-Cog: memory score	4.4 (2.7)	15.8 (8.8)[c]
ADAS-Cog: language score	1.0 (1.2)	4.8 (4.8)[c]
ADAS-Cog: Praxis score	0.5 (0.6)	3.2 (4.1)[c]
ADAS-Cog: total score	6.0 (3.5)	23.7 (16.4)[c]
EEG: complexity (T5)	1.2674 (0.0074)	1.2593 (0.0116)[c]
EEG: complexity (T6)	1.2672 (0.0067)	1.2604 (0.0132)[c]
EEG: complexity (O1)	1.2692 (0.0094)	1.2572 (0.0130)[c]
EEG: complexity (O2)	1.2679 (0.0083)	1.2599 (0.0108)[c]
EEG: delta and theta power (%); (Mody et al., 1991)	39.9 (15.1)	52.9 (18.1)[c]
EEG: alpha and beta power (%); (Mody et al., 1991)	60.1 (15.1)	47.1 (18.1)[c]
EEG: right temporal theta/(alpha+beta); (Bennys et al., 2001)	0.38 (0.37)	0.62 (0.53)[b]
EEG: left temporal theta/(alpha+beta); (Bennys et al., 2001)	0.35 (0.45)	0.62 (0.50)[b]
EEG: right posterior theta/(alpha+beta); (Bennys et al., 2001)	0.32 (0.37)	0.58 (0.51)[b]
EEG: left posterior theta/(alpha+beta); (Bennys et al., 2001)	0.32 (0.30)	0.58 (0.46)[b]
EEG: regression of coherence and amplitude; (Brunovsky et al., 2003)	17.98 (4.15)	15.73 (4.60)[a]
EEG: log relative beta activity (T5O1); (Claus et al., 1998)	−1.49 (0.70)	−1.54 (0.70)
EEG: log relative beta activity (T6O2); (Claus et al., 1998)	−1.10 (0.68)	−1.51 (0.68)
EEG: log relative beta activity (P3O1); (Claus et al., 1998)	−1.49 (0.73)	−1.50 (0.70)
EEG: log relative beta activity (P4O2); (Claus et al., 1998)	−1.51 (0.73)	−1.49 (0.71)
EEG: mean frequency (C3P3); (Lopez et al., 1997)	10.31 (1.27)	9.68 (1.58)[a,d]
EEG: mean frequency (C4P4); (Lopez et al., 1997)	10.28 (1.27)	9.68 (1.55)[a]
EEG: mean frequency (P3O1); (Lopez et al., 1997)	10.31 (1.33)	9.76 (1.63)
EEG: mean frequency (P4O2); (Lopez et al., 1997)	10.31 (1.35)	9.82 (1.61)
At EEG recording: hours since last meal	2.32 (2.47)	2.45 (3.23)
At EEG recording: degree of alertness (1–5 alert)	4.05 (0.79)	3.88 (0.91)
At EEG recording: hours of sleep night before	6.97 (1.19)	7.52 (1.71)
Caffeine servings per day	2.07 (1.78)	2.10 (2.25)
Nicotine servings per day	0.23 (1.44)	0.03 (0.17)

Values = means (S.D.).
[a] $P<0.05$ vs. normal by ANOVA.
[b] $P<0.01$.
[c] $P<0.001$.
[d] Age as covariate has significant effect ($P<0.05$).

Table 2
Dementia risk analysis (factors collected from questionnaire, interview, and records).

Factor	Odds ratio	Lower 95% CI	Upper 95% CI
Patient has ≥3 of selected cardiovascular risks (†)	11.4	2.5	50.9
† Transient ischemic attacks	8.5	3.0	23.8
† Untreated diabetes	5.0	0.4	56.8
Age (70–85 vs. 55–70)	4.8	1.7	13.7
Anxiety self rating>5; (0–10 anxious)	4.2	1.3	13.9
† History of alcohol abuse	4.1	1.1	15.7
† Stroke	3.4	0.7	16.4
† Alcohol abstention	3.1	1.3	7.5
† Hypertension	3.0	1.2	7.4
† Chronic obstructive pulmonary disease	2.5	0.5	13.1
† Myocardial infarcts	2.4	0.8	7.2
† Not married	2.3	1.0	5.2
Surgery > 70 years	2.1	0.9	5.3
† Hypercholesterolemia (requiring medication)	2.1	0.9	4.8
Antidepression medication (past and/or present)	1.9	0.8	4.3
† Gender: male	1.7	0.7	3.8
† Overweight by body mass index	1.6	0.7	3.7
† Significant arterial blockage	1.6	0.6	4.7
† Diabetes	1.6	0.6	4.3
Sleep: always has difficulty falling asleep	1.4	0.5	3.3
Depression self rating >5; (0–10 depressed)	1.3	0.3	5.3
Family history of depression	1.2	0.5	2.9
Sleep: has daytime drowsiness	1.2	0.5	2.7
Asthma	1.2	0.4	3.9
† Emphysema	1.2	0.3	5.1
Polio	1.2	0.1	13.6
History of hypercholesterolemia	1.1	0.5	2.5
Peripheral vascular disease	1.1	0.4	3.2
Sleep: always recalls dreams	1.1	0.4	3.0
Headaches or migraines	1.0	0.4	2.4
Past toxic exposure (metal, CO, insecticides, molds)	0.8	0.3	1.9
Education — greater than high school	0.8	0.4	1.9
Family history of anxiety	0.8	0.3	2.2
History of convulsions or seizures	0.8	0.1	7.8
Allergies (food, environmental)	0.7	0.3	1.6
Bacterial illnesses	0.7	0.2	2.6
Sleep: difficulty staying asleep	0.6	0.3	1.6
Gastrointestinal problems	0.6	0.2	1.4
Family history of alcoholism	0.6	0.3	1.5
Cancer	0.6	0.3	1.5
History of metal in mouth	0.6	0.2	1.5
Traumatic brain injury	0.6	0.3	1.5
Thyroid imbalances (requiring medication)	0.6	0.3	1.6
Chronic pain	0.6	0.3	1.4
Bronchitis	0.5	0.2	1.2
Untreated hypercholesterolemia	0.5	0.2	1.3
Use of caffeine	0.5	0.2	1.3
History of thyroid imbalances	0.5	0.2	1.4
Race: Caucasian	0.4	0.1	1.1
History of childhood or adolescent abuse or trauma	0.3	0.1	1.3
Viral illnesses	0.2	0.0	1.7
Hormone replacement therapy	0.2	0.1	0.6

CI = confidence interval.

a post-doctoral geriatric-psychology fellow (over four years of experience administering EEG collection and psychology tests) supervised by an attending senior psychologist. For cardiovascular history, the fellow conducted questionnaires, interviews, and medical record reviews and then documented patient characteristics and risk factors.

During the same visit, the fellow recorded EEG (DCS; Lexicor, Augusta, GA). Planned EEG analyses (Sections 2.4, 2.5) required the International 10–20 system which was applied by electrode cap (ground electrode near FZ; linked ears reference). Electro-oculography was used to monitor eye movement. Electrode impedances were adjusted (≤10 kΩ). EEG specifications included 128 Hz sampling rate, 60 Hz notch filter, and band pass down 3 dB at 0.5 and 36 Hz. Ten minutes (300 epochs) of eyes-closed data were collected. As part of the standardized processing, one or more trained EEG technicians (each with training and certification by the device manufacturer) performed manual artifacting by visual detection.

2.4. Linear EEG analysis

Linear analysis of EEG was conducted using Fast Fourier Transform analysis (frequency resolution: 0.5 Hz). We planned to investigate previously documented EEG variables associated with dementia: 1) delta and theta absolute power at T5, T6, P3, P4, O1, O2 (Mody et al., 1991); 2) alpha and beta absolute power at T5, T6, P3, P4, O1, O2 (Mody et al., 1991); 3) power ratio of theta/(alpha+beta1) at regions: right temporal (F8T4T6), left temporal (F7T3T5), right posterior (T4T6O2) and left posterior (T3T5O1) (Bennys et al., 2001); 4) regression equation of alpha and delta coherence and alpha amplitude from temporal, occipital and frontal sites (Brunovsky et al., 2003); 5) log relative beta activity using bipolar derivations (T5O1; T6O2; P3O1; P4O2) (Claus et al., 1998); and 6) mean frequency for 1–30 Hz using bipolar derivations (C3P3; C4P4; P3O1; P4O2) (Lopez et al., 1997).

2.5. Non-linear EEG analysis

For non-linear EEG analysis, the fractal dimension was determined using a Box Counting algorithm (Gonzato, 1998; Weisstein, 2002; Roy et al., 2007). Whereas other non-linear methods have been applied to dementia with relative success (Hornero et al., 2009), the fractal dimension was selected because it has been associated with AD in an autopsy-confirmation study (the gold standard for AD), and the fractal dimension is considered to be representative of a shift in power to lower frequencies (the most commonly reported EEG change in AD) (Woyshville and Calabrese, 1994). Furthermore, the Box Counting algorithm was selected because it has been widely used in other fields to determine the fractal dimension, and it is considered to be practical and efficient (Henderson et al., 2006; Roy et al., 2007). The technique involves covering a time series with a shrinking grid and counting the number of boxes that contain at least one point. The Box Counting algorithm requires a relatively large number of data points (Hornero et al., 2008); however time lengths greater than 2 s are known to produce results affected by the nonstationarity nature of EEG data (Henderson et al., 2006). Therefore the 2 second epochs of the current study represent the best possible tradeoff between sufficient data for the Box Counting algorithm and approximate stationarity (Lehnertz et al., 2003). The technique was performed on each epoch included after artifacting. Time was normalized to units of 2 s. Voltage was normalized by first subtracting the minimum data point from a given value, and then dividing the result by the data range. A grid was laid over the entire data set for the epoch under analysis, and the number of boxes containing a point was calculated for each side length. To obtain a reliable result, a large range of side lengths must be used and should, as a general rule, span at least three orders of magnitude (Gonzato, 1998). For a 256-point epoch, the optimal range for the grid scale is ¼ to 1/32, giving from 16 to 1024 boxes, reduced by a factor of 2 each time (¼, 1/8, 1/16, 1/32). When the results are plotted as ln(number) vs. ln(1/side length), the slope is the estimate of the fractal dimension for that epoch. The process was repeated for each included epoch. Complexity was the average of fractal dimensions of each epoch, determined separately for O1, O2, T5, and T6.

2.6. Statistical analysis

We hypothesized that accuracy of logistic models would improve when EEG is included. Models were constructed using logistic regression to integrate planned variables from 1) neuropsychological testing, 2) cardiovascular history, and 3) biological data (EEG or MRI); accuracy and R^2 values were produced. To support the validity of integrating the model variables, we selected the apparent optimal model for the investigated variables and then performed further analyses. First, goodness of fit was determined using the Hosmer–Lemeshow statistic ($P>0.05$). Second, Nagelkerke R^2 was evaluated. Third, ANOVA (two-tailed; significance level 0.05) determined whether each variable was significantly different between dementia and normal (with age included as a covariate when significant). Fourth, inclusion of variables was evaluated by forward and backward stepwise logistic regression; contribution of variables was examined by 2-log-likelihood ($P<0.05$). Fifth, split-half random sampling was used for cross-validation. Finally, receiver-operating characteristic (ROC) analysis determined accuracy over a range of cutoffs. Further analyses of the sample included one-way ANOVA (two-tailed; significance level 0.05) to investigate between group differences (dementia vs. normal) in demographics. Odds ratio analysis was used to evaluate binary factors of risk and demographics.

3. Results

3.1. Accuracy of logistic models

We found that addition of EEG improves the accuracy of a logistic model that uses both neuropsychological assessment and cardiovascular history to identify dementia and MCI as a single group (Table 3). Note that the model identifies a general 'dementia and MCI' group that includes AD, VAD, mixed dementia, and MCI, but the model does not differentiate between the subgroups. As such the model

Table 3
Planned logistic models for dementia.

Neuropsychological testing	Cardiovascular history	Biological data	R^2	Overall accuracy (%)
ADAS-Cog: praxis	None	None	0.193	60.4
ADAS-Cog: language	None	None	0.193	60.4
ADAS-Cog: memory	None	None	0.277	65.8
ADAS-Cog: total	None	None	0.288	64.9
ADAS-Cog: total	Cardiovascular risk factors[a]	None	0.534	80.2
ADAS-Cog: total	Cardiovascular risk factors[a]	MRI/CT interpreted by specialist	0.563	81.1
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Left posterior theta/(alpha+beta)[b]	0.611	81.1
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Left temporal theta/(alpha + beta)[b]	0.614	79.3
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Right posterior theta/(alpha+beta)[b]	0.634	80.2
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Right temporal theta/(alpha+beta)[b]	0.665	82.0
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Delta and theta power (%)[c]	0.707	85.6
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Regression of coherence & amplitude[d]	0.766	88.3
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Alpha and beta power (%)[c]	0.768	87.4
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Mean frequency (C3P3)[e]	0.781	89.2
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Mean frequency (C4P4)[e]	0.782	88.3
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Complexity (O2)	0.818	91.9
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Complexity (O1)	0.818	91.9
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Complexity (T6)	0.819	91.9
ADAS-Cog: total	Cardiovascular risk factors[a]	EEG: Complexity (T5)	0.820	91.9

[a] Summed set, see Table 2.
[b] Bennys et al. (2001).
[c] Mody et al. (1991).
[d] Brunovsky et al. (2003).
[e] Lopez et al. (1997).

represents characteristics common to all of the subgroups. A series of planned classification models were constructed and analyzed by logistic regression. Logistic models containing ADAS-Cog memory or total scores offered increased R^2 values and accuracies over those containing ADAS-Cog praxis or language scores. Integration of a summed set of cardiovascular factors (Table 2) with ADAS-Cog total score improved accuracy and R^2 results (Table 3). Addition of MRI/CT (interpreted by a specialist for lesions) offered no improvement to a logistic model containing neuropsychological testing and cardiovascular factors. Individual EEG variables that demonstrated significant differences between dementia and normal (Table 1) offered improvement to the logistic models (Table 3). For instance, addition of EEG (non-linear complexity) to a model that included both neuropsychological assessment (ADAS-Cog total score) and cardiovascular factors increased accuracy from 80% to 92% and increased R^2 from 0.53 to 0.82. Further addition of any of the investigated linear EEG variables offered no improvement to a logistic model containing a non-linear EEG variable (complexity, T5), neuropsychological testing, and cardiovascular factors (not shown).

3.2. Validity of integration

To further investigate the validity of integrating the assessment methods, we selected the apparent optimal model (of the investigated variables) for identification of dementia and MCI as a single group and then performed a further series of analyses. In our limited sample, the optimal logistic model involved integration of: 1) ADAS-Cog total score, 2) summed set of 15 cardiovascular risk factors (Tables 2 and 3) non-linear analysis of EEG complexity at T5 (Table 3). This specific model was further analyzed to evaluate statistical support for data integration.

First, the Hosmer–Lemeshow statistic had a P-value of 0.98 which verifies that the model did adequately fit the data. Second, the Nagelkerke R^2 statistic was 0.82, which indicates that the majority (82%) of the variation in our dementia/normal sample is explained by the model predictors. Third, ANOVA demonstrated that each variable was significantly different between dementia and normal: EEG complexity at T5 ($F_{1,109} = 19.74$, $P<0.0001$), ADAS-Cog total score ($F_{1,109} = 83.66$, $P<0.0001$), and cardiovascular factors ($F_{1,109} = 19.01$, $P<0.0001$), supporting that each variable can contribute to the model (however it should be noted that such a requirement is not mandatory for logistic models).

Fourth, forward-stepwise logistic regression verified that inclusion of each variable in the model is statistically valid. This automated method selected variables in succession by largest score statistic with significance value <0.05, which reduces the possibility of overfitting. The model was further verified using backward-stepwise logistic regression, which statistically selected the same variables, indicating an effective model of the data. The contribution of each variable was further verified by significant changes in 2-log-likelihood ($P<0.05$).

Fifth, validity of the model was assessed using random split-half sampling to develop and cross-validate with separate samples. The consistency of accuracy results supports that the selected variables are appropriate and the model is well fit (Table 4). Sixth, the accuracy of the model was evaluated using ROC analysis (standard probability cutoff = 0.5). The area under the ROC curve was 0.96 indicating a 96% probability that a randomly chosen dementia or MCI patient will have a higher probability score than a randomly chosen normal adult.

The above statistical analyses support the validity of integrating neuropsychological testing, cardiovascular history, and EEG in a logistic model to identify dementia and MCI. The logistic model identified dementia and MCI as a single group comprised of the following subgroups (with accuracies): Alzheimer's disease (92%; 12/13), vascular dementia (73%; 8/11), mixed dementia (100%; 4/4), and MCI (80%; 4/5). The applicability of the model to multiple forms of dementia as well as MCI implies that the subgroups share a reasonably strong association with the model variables (neuropsychological assessment, cardiovascular factors, and EEG complexity).

4. Discussion

The results of this pilot study support that the addition of EEG improves the accuracy of a logistic model that uses both neuropsychological assessment and cardiovascular history to identify dementia

Table 4
Cross-validation (random split-half sampling) of selected logistic model[a].

Sample	Sensitivity (%)	Specificity (%)	Overall accuracy (%)
Total sample	85	95	92
1st Random split-half; development	83	97	93
1st Random split-half; cross-validation	87	90	89
2nd Random split-half; development	80	94	90
2nd Random split-half; cross-validation	89	96	94

[a] ADAS-Cog total score, summed set of 15 cardiovascular risk factors, and EEG complexity at T5.

and MCI as a single group. We found that the addition of EEG (non-linear complexity) increased overall accuracy from 80% to 92%. Whereas the analysis is limited by small sample sizes and mixing of diverse pathologies, the use of a logistic model to identify dementia subtypes and MCI as a single group does provide support that the subgroups may share changes in neuropsychological, cardiovascular, and electroencephalographic factors (specifically ADAS-Cog total score, cardiovascular history, and EEG complexity).

Whereas EEG and neuropsychological testing have been examined together in previous studies (Jelic et al., 2000; Lindau et al., 2003), to our knowledge the current study was novel in the additional integration of cardiovascular history. Previous studies have combined EEG with neuropsychological testing for identification of MCI, AD, and frontotemporal dementia (Jelic et al., 2000; Lindau et al., 2003). With the addition of cardiovascular history, logistic models of the current study identified dementia and MCI as a single group which included AD, VAD, mixed dementia, and MCI. The implication is that these subgroups have in common an integrated spectrum of neuropsychological symptomology, cardiovascular changes, and abnormal neural activity in the cortex. In terms of cardiovascular changes, the implication of shared factors between subtypes is consistent with recent studies which supported that the cardiovascular system is not only important in the development of VAD, but also AD and MCI. In fact, the main risk factors for AD and MCI have also been found to be risk factors for cardiovascular disease (Breteler, 2000; Meyer et al., 2000a; de la Torre, 2004; Nash and Fillit, 2006).

Furthermore, the contribution of linear EEG to the logistic model might be related to cardiovascular changes. Linear EEG variables that offered improvement to the logistic model are indicators of EEG slowing, a shift to lower frequency activity. The observation of EEG slowing and cardiovascular risk factors in dementia patients of the current study is consistent with previous findings that EEG slowing is correlated with cerebrovascular changes such as hypoperfusion associated with dementia and MCI (Jelic et al., 2000; Mattia et al., 2003; Meyer et al., 2000b; Rodriguez et al., 2004).

When non-linear EEG complexity is included, improvement of accuracy may imply representation of further information than that associated with cardiovascular changes. Previous studies suggest that reduced complexity may be the result of neuronal death, neurotransmitter deficiency, and loss of connectivity of local neural networks due to cell death (Jeong, 2004; Abasolo et al., 2006). Furthermore, previous studies have shown that adding linear EEG to non-linear EEG alone improves classification accuracy for AD and normal subjects (Pritchard et al., 1994; Hornero et al., 2009). However in the current study, addition of linear EEG did not offer further improvement to a logistic model containing non-linear complexity when neuropsychological testing and cardiovascular factors were included as well. It cannot be ruled out that EEG slowing may be related to decreased complexity in AD (Jeong, 2004), and the current results support that non-linear analysis might optimize the value of EEG when combined with cardiovascular factors and neuropsychological testing in identifying dementia and MCI as a single group.

Whereas the study sample was too small to allow precise determination of accuracy for the subgroups, it is still of interest that a logistic model which included cardiovascular risk factors had the lowest accuracy for vascular dementia. We speculate that this result may be due to the fact that VAD is a heterogeneous group of disorders having causes that may involve focal lesions, small vessel disease, or multifocal lesions. Such lesions affect strategic areas of the brain and lead to deafferentation of frontal and limbic systems followed by interruption of thalamo- and striatal- cortical pathways reflecting damage in basal ganglia, thalamus or white matter (Jellinger, 2005). The variability in lesions may have reduced the potential to identify VAD in the proposed models. A larger clinical sample than in the current study would be required to examine the effect of this variability.

4.1. Limitations

The small sample of the current study not only limited precise examination of subgroups, but also limited generalizability of the overall results. Generalizability was also limited by the relative demographic homogeneity of the overall sample. The small sample also left open the possibility of overfitting in the model development. Additional research on larger more heterogeneous samples would be useful in further investigating the integrative approach.

Our selected reference standard presented another potential limitation to the study. The reference standard included some information (neuropsychological assessment and MRI) overlapping with the logistic regression analyses, which could lead to standard bias and circular proof with those specific elements. However the reference standard (dementia diagnosis) was ultimately based on clinical judgment of a geriatric physician. ADAS-Cog alone only identified 65% of the geriatric physician's diagnoses, and MRI did not contribute to a logistic model containing ADAS-Cog and cardiovascular factors. The overall goal of this pilot study was to determine contribution of EEG which importantly was not part of the reference standard.

A further limitation of the reference standard was that only one geriatrician performed the diagnosis per patient. A study of classification models is dependent on the accuracy of the reference standard, and there is no definitive reference standard for AD, VAD, mixed dementia, and MCI. The inclusion of more geriatricians with a variety of expertise might improve the precision of the study results, and should be considered for future work.

Our study of EEG variables was limited to a few linear variables and only one non-linear variable. Within this selection, we observed a variation in accuracy from 79% to 92%. These results show that the choice of EEG variable can indeed have an effect on the accuracy of the logistic model. In the current study the choice of EEG variable has by no means been definitively optimized. Considering the relatively large number of linear and non-linear EEG variables previously applied to dementia (Jeong, 2004; Stam, 2005; Hornero et al., 2009), future studies might determine which EEG variable provides the greatest improvement in accuracy.

For non-linear EEG analysis, the fractal dimension was determined using a Box Counting algorithm (Gonzato, 1998; Weisstein, 2002; Roy et al., 2007). This method is limited by the requirement of a relatively large number of data points balanced against the likelihood of nonstationarity at time lengths greater than 2 s (Lehnertz et al., 2003; Henderson et al., 2006; Hornero et al., 2008), whereas other non-linear methods are reported to be less restricted (Hornero et al., 2009). Regardless of the limitations of the current method, reliability was supported by the consistency of accuracy results in random split-half sampling (Table 4). The current results are also consistent with previous findings in which the fractal dimension was associated with AD per autopsy-confirmation, the gold standard for AD (Woyshville and Calabrese, 1994).

A final limitation of the study was that the sampling and methodology restricted the application of neuroimaging (i.e. MRI). The contribution of neuroimaging to the logistic model might have been improved by the use of more complex data such as hemodynamic changes (Mattia et al., 2003). Neuroimaging may have had a stronger contribution if applied to samples in which focal neurological signs and clinical presentation suggested the need to identify space-occupying pathologies such as tumor, stroke or normal pressure hydrocephalus (Wahlund et al., 2005). Neuroimaging might also have offered an improved contribution in the assessment of patients with very advanced age (Mueller et al., 2006).

4.2. Conclusions/implications

In conclusion, the pilot study does offer support that addition of EEG can improve the accuracy of a logistic model that uses neuropsychological

assessment and cardiovascular history to identify dementia and MCI as a single group. Because cardiovascular history and neuropsychological testing were incorporated to an extent in the study's reference standard, the improvement in accuracy provides support that EEG in particular may offer additional information that might complement the clinician's evaluation of dementia and MCI.

Of note is that the logistic model was applicable to a variety of dementia subtypes as well as to MCI. Clinically, the ability to distinguish MCI from normal aging is important in the early detection of AD and other dementias. Related EEG studies have shown some success; for instance EEG dipole analysis differentiated AD from MCI with 78% accuracy but could not discriminate MCI from normal adults (Huang et al., 2000). In comparison, the current logistic model was accurate for 80% of the MCI subgroup and 95% of normal adults. As such, the integration of neuropsychological data, cardiovascular factors and non-linear EEG complexity is promising and warrants further investigation in the differentiation of early cognitive decline from normal aging.

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