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The use of EEG in Alzheimer's disease, with and without scopolamine – A pilot study

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ABSTRACT

Objective: To use multivariate statistical analysis of EEG data in order to separate EEGs of patients with Alzheimer's disease (AD) from controls. A group of individuals with mild cognitive impairment (MCI) was evaluated using the same methodology. Additionally, the effects of scopolamine on this separation are studied.
Methods: Statistical pattern recognition (SPR) is used in conjunction with information extracted from EEGs before and after administration of scopolamine.
Results: There was complete separation of the AD group and controls before administration of scopolamine. The separation increased after scopolamine had been given. Of the 10 MCI individuals, five seemed to belong to the AD group. Three of those progressed to AD within 1 year and one after 3 years.
Conclusions: Using SPR on EEG recordings it is possible to separate AD from controls. This separation can be increased by the use of scopolamine but the medication is not a prerequisite for classification. The results indicate that SPR is useful for predicting progress of MCI to AD.
Significance: EEG registration is a simple and noninvasive method. If these results are confirmed in other studies, this method could be more widely applied than the highly specialized methods used today in detection of early AD.

1. Introduction

Alzheimer's disease (AD), first described in 1906, is the most common neurodegenerative disease of humans with more than 20 million cases worldwide (Goedert and Spillantini, 2006). The initial stage of AD is cognitive impairment without dementia, most often referred to as mild cognitive impairment (Petersen, 2004). This stage is however not defined as being part of AD since many individuals fulfilling the MCI criteria will not progress to full blown AD. It is therefore important to correctly characterize those individuals who will progress further and those who will remain stable. This can best be done by using some kind of a biomarker. Several biomarkers for AD have been tested for diagnostic purposes of the disease as well as correctly identifying those patients with MCI who will later progress to full blown AD. The best known are changes in volume of the hippocampus and the medial temporal lobe on MRI, FDG-PET (positron emission tomography with fluorodeoxyglucose), neuropsychological evaluation and cerebrospinal fluid (CSF) analysis of beta amyloid and tau proteins but these methods are highly specialized and some are invasive. These methods are therefore not in widespread use outside the most advanced centers (Knopman et al., 2003). A more simple biological marker making it possible to diagnose AD in the preclinical phase could be more generally applicable as well as being helpful in the development of disease-modifying therapies (Nestor et al., 2004).

In this regard the EEG, particularly quantitative EEG (qEEG), has been evaluated and there is some evidence that MCI patients who progress to AD have different EEG from those who do not (Winblad et al., 2004).

EEG abnormalities are frequently shown in cortical dementias like AD and EEG has been used to study AD since Hans Berger's research in the early 1930s (Jeong, 2004). It should be noted, however, that healthy elderly also undergo EEG changes during aging and it is important to take that into consideration. The hallmark of EEG changes due to AD is a general slowing and decrease of alpha activity which leads to increased theta activity. Cognitive decline also leads to changes in higher frequency components, in particular in the occipital and temporal areas. These changes have been shown to correlate with severity of the disease (Jeong, 2004).

Instrumentally, measuring EEG is much less elaborate than MRI or FDG-PET. Therefore the training of clinical staff to handle the EEG measurements takes less time and is not as costly. The analysis of EEG data is, however, not simple. In our analysis we apply a Statistical Pattern Recognition (SPR) technique to a multitude of EEG features to separate two groups of EEG measurements. This is by no means a simple task and requires substantial technical

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knowledge, but the interpretation of the results is simple. Until now the use of EEG in the clinical setting of AD diagnosis has suffered from the fact that using only one feature or two of the EEG to separate the AD group and the control group has been inadequate, as the accuracy does not exceed 80% and the overlap of feature densities between the groups is too great to be of clinical use (Jeong, 2004). The purpose of this investigation is to check whether it is possible to use multiple EEG features with SPR analysis on small sets of EEG measurements from AD patients and controls to separate the two groups. Furthermore we want to see if it is possible to use this method to predict which MCI patients will later develop AD. If the results of this pilot study are promising, a large study will be launched.

The cholinergic system deteriorates in AD and this knowledge led to the development of the cholinergic hypothesis (Coyle et al., 1983; Terry and Buccafusco, 2003) to account for the cognitive decline in AD. It has been postulated that the cholinergic deficit also accounts for the EEG slowing (Agnoli et al., 1983). The reversal of EEG slowing by cholinergic drugs supports this (Jeong, 2004). Scopolamine, a muscarinic cholinergic antagonist, has been suggested as a candidate for use in a model of AD dementia although it is known that other neurotransmitters than acetylcholine are involved (Nobili and Sannita, 1997; Ebert and Kirch, 1998). Analysis of neuropsychological test scores has shown that young subjects who were cholinergically "blocked" with scopolamine had a test performance pattern similar to mild AD patients while their performance pattern did not mimic the pattern of AD patients as a group (Christensen et al., 1992). Scopolamine has been shown to affect the EEG delta, theta, alpha and beta activity in a similar manner as the changes observed in AD patients (Ebert and Kirch, 1998). This supports the hypothesis that the EEG changes are linked to the decreased cholinergic activity. The half-life of scopolamine is short and its effect is quite rapid peaking 1–3 h after administration and disappearing 5–6 h after subcutaneous administration (Ebert and Kirch, 1998). In a previous study at our laboratory it was shown that by using scopolamine hydrobromide 0.3 mg intravenously there was a decrease in the relative power of the alpha band in the first ten minutes after substance administration. This effect did not occur using placebo (Johannesson et al., 2003). Scopolamine has different effects on the EEG of AD patients and controls, probably reflecting the reduced cholinergic tone in AD (Neufeld et al., 1994). Scopolamine, like other muscarinic antagonists, causes mydriasis (pupil dilatation). This can increase intra-ocular pressure which subsequently can result in acute angle-closure glaucoma (Eskandar et al., 2005). This risk must be taken into consideration.

We hypothesized that scopolamine might enhance the accuracy of EEG in AD diagnosis thus making EEG a more clinically useful tool.

2. Methods

2.1. Subjects

The subjects belonged to three distinct groups, consisting of 10 recently diagnosed AD patients, 10 subjects with MCI and 10 age-matched controls. The former two groups of participants were patients in follow-up at the Memory Clinic, Geriatric Department of Landspitali University Hospital in Reykjavik, Iceland. The third group, the controls, was recruited from relatives of demented patients attending a day-care center. One control subject was excluded from the EEG analysis due to concealed information (alcohol abuse) which surfaced after the conclusion of the trial.

To be eligible for participation in the study the subject had to be 60–80 years of age, in good general health as determined by standard physical examination and with no substantial changes on electrocardiogram (ECG). Exclusion criteria were smoking or any other use of tobacco in the 7 days prior to EEG, treatment with neuroleptics or benzodiazepines, impaired liver or kidney function, hypersensitivity to scopolamine, indication of drug or alcohol abuse, glaucoma or a narrow angle increasing the possibility of raised intra-ocular pressure with administration of scopolamine. Prior to the screening visit the subjects were interviewed by phone and evaluated clinically by an opthalmologist. Eight persons (3 controls, 3 AD and 2 MCI) were excluded due to glaucoma or risk of angle-closure glaucoma with the administration of scopolamine. Three persons (one in each group) did not finish their participation in the study after the screening visit due to personal reasons. These 11 participants were replaced according to protocol.

The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria (McKann et al., 1984). The AD patients had mild to moderate disease rated according to global deterioration scale (GDS), stages 4–5 (Reisberg et al., 1982). All the patients were living in their homes. When the AD patients were evaluated, all had undergone single photon emission computed tomography (SPECT) and morphologic radiology (CT/MRI). The diagnosis of MCI, using F06,7 according to ICD-10, was based on a history of cognitive decline, verified by a relative, without reaching the level of dementia. Clinically, these patients were in GDS stages 2–3. Participants in the control group had to have no history of cognitive decline and a mini-mental state exam (MMSE) (Folstein et al., 1975) score of at least 26 points out of 30. The MMSE has been translated into Icelandic and validated (Tómasson, 1986), however a revised version was used (Snædal et al., 1997). The characteristics of the participants are shown in Table 1.

To minimize variability, all the AD patients were treated with the same acetylcholinesterase inhibitor, galantamine (Reminyl®). One MCI patient receiving rivastigmine (Exelon®) did not use it for 2 weeks prior to EEG recording. One control receiving chlordiazepoxide and clidinium (Librax®) did not use it for 5 days prior to EEG recording. The trial adhered to the Declaration of Helsinki and written informed consent was obtained. The study was approved by the Icelandic National Bioethics Committee (Ref.: VSN2004010004).

2.2. EEG

The EEG was recorded for 2 min during rest with eyes closed before and approximately 7 min after scopolamine administration. Each subject received 0.3 mg of scopolamine in a 1 mL saline solution intravenously. The 10–20 system was used to place electrodes at the following positions: Fp1, Fp2, F3, F4, F7, F8, Fz, T3, T4, T5, T6, A1, A2, C3, C4, Cz, P3, P4, Pz, O1, O2 and Oz. Fpz was used as reference. Two bipolar electrooculography channels and one ECG were applied to monitor artifacts. The subjects were alerted if they became visibly drowsy. The sampling rate was 1024 Hz. The amplifier has a low pass anti-aliasing filter with a cutoff frequency at 268 Hz. The EEGs were obtained with the NicoletOne nEEG Module from VIASYS Healthcare Inc. Subsequent analysis was done in a Matlab environment from The MathWorks.

2.3. Data analysis

The Maximum Entropy Spectral Analysis (MESA) (Burg, 1975) method was used to estimate the spectral features of the EEG

Table 1
Characteristics (averages ± standard deviation in last three columns) of the participants. The MMSE has a maximum score of 30.

Group	Male	Female	Age	GDS	MMSE (30)
Controls	2	7	72.2 ± 5.3	1.2 ± 0.4	29.1 ± 0.9
MCI	4	6	74.3 ± 3.2	2.4 ± 0.5	27.7 ± 2.2
AD	7	3	75.9 ± 3.0	4.3 ± 0.5	21.2 ± 2.6

and the resulting spectra had a 0.5 Hz resolution. Typical examples of EEG spectra from the control and AD groups are shown in Fig. 1.

The data was analyzed using a Statistical Pattern Recognition (SPR) technique which was applied to a set of EEG features extracted from each EEG. The type of SPR method used here is called Support Vector Machine (SVM) (Duda et al., 2001).

The reliability of the EEG features used in this study has already been investigated (Gudmundsson et al., 2007). A brief description of those features is given in Table 2. A more detailed description of the features and how they are calculated can be found in (Gudmundsson et al., 2007) and references therein. A total of 28 features are extracted from each of the 22 EEG channels, resulting in a set of 616 features. The set of chosen features defined the abstract data space considered in the classification problem. During the training phase the strategy was to work with known data which was preclassified into relevant groups. Here we considered a binary problem indicating that we worked with 2 groups. The training phase consisted of determining the optimal decision boundary (ODB) that best separates the 2 groups in the feature space. A two-dimensional representation is shown in Fig. 2 using the two main principal components as axes. Furthermore, an index was generated for each individual of both groups which was based on the distance from the ODB. This index represents which group the EEG belongs to: a value of 0 means that the EEG is indistinguishable from the EEGs in the AD group and a value of 1 means that the EEG is indistinguishable from the EEGs in the control group. The contour plot in Fig. 2 gives the value of this index, thus the contour line where the value of the index is 0.5 is the ODB. Each new data was then represented by a point in this space as seen in Fig. 3 for the group of MCI individuals. The classification of the MCI group was based on which side of the ODB the individuals in the group fall.

Table 2
Features extracted from the EEG for the statistical pattern classifier. A short description of each feature is given.

No.	Description
1	Power in the δ frequency band (0.5–3.5 Hz)
2	Power in the θ frequency band (3.5–7.5 Hz)
3	Power in the α_1 frequency band (7.5–9.5 Hz)
4	Power in the α_2 frequency band (9.5–12.5 Hz)
5	Power in the β_1 frequency band (12.5–17.5 Hz)
6	Power in the β_2 frequency band (17.5–25 Hz)
7	Power in the γ frequency band (25–40 Hz)
8	Relative power in the δ frequency band
9	Relative power in the θ frequency band
10	Relative power in the α_1 frequency band
11	Relative power in the α_2 frequency band
12	Relative power in the β_1 frequency band
13	Relative power in the β_2 frequency band
14	Relative power in the γ frequency band
15	Total power of the EEG power spectrum (0.5–40 Hz)
16	Peak α frequency
17	Median frequency of the EEG power spectrum
18	Spectral entropy
19	Power ratio: $\theta/(\alpha_1 + \alpha_2 + \beta_1)$
20	Power ratio: $(\delta + \theta)/(\alpha + \alpha_2 + \beta_1 + \beta_2)$
21	Power ratio: $\theta/(\alpha_1 + \alpha_2)$
22	Activity: variance of the EEG signal
23	Mobility: variance of the first derivative of the EEG signal
24	Complexity: variance of the second derivative of the EEG signal
25	Sample entropy
27	Permutation entropy
28	Lempel–Ziv complexity

3. Results

Fig. 2 shows the AD/control classifier using the two main principal components resulting from the SPR analysis of the two groups. We obtained complete separation of the groups using our statistical pattern classifier approach without the use of scopolamine. We found that features strongly correlated to the alpha generator (the source of the alpha activity) best discriminate between the groups. This was confirmed by a strong correlation between the two principal components and the power in the alpha and theta frequency bands in the two groups of EEGs. This finding is consistent with the slowing of the EEG in AD patients represented by a larger shift of power from the alpha frequency band into the theta frequency band when compared to controls (Jeong, 2004).

Then the same calculations were used for the individuals in the MCI group leading to Fig. 3 where all the subjects are placed according to their principal component values. As expected, the

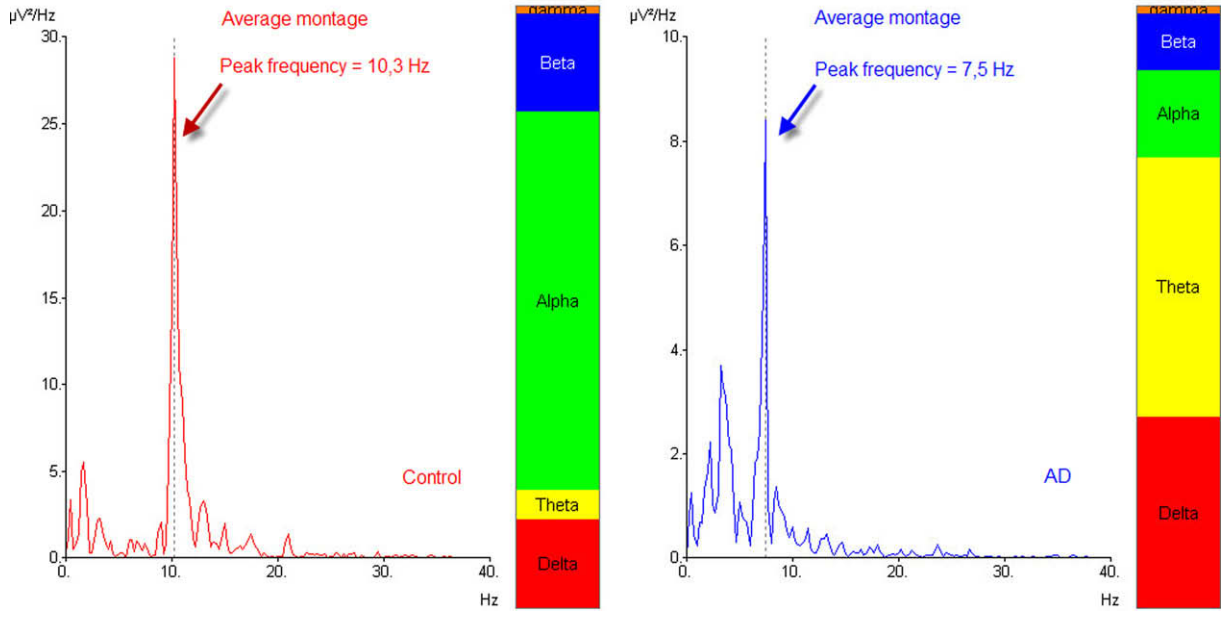

Fig. 1. Examples of EEG frequency spectra from the AD and control groups. The relative powers of the individual frequency bands are displayed on the bars on the right hand side of each spectrum. The frequency bands are: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–25 Hz) and gamma (>25 Hz).

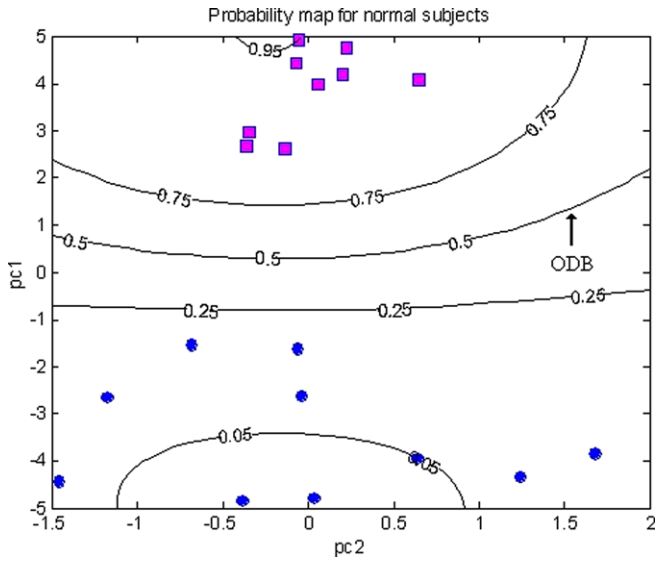

Fig. 2. A two-dimensional representation of the results of the SPR analysis of the two groups of EEG features, AD and control. The nine squares are the control group and the 10 circles are the AD group. The axes represent the two principal components of a collection of EEG features that best separate the two groups. The underlying contour plot is the value of an index generated by the analysis. The index has a value of 0.5 in the ODB. The range of the index is from 0 (EEG features indistinguishable from the EEG features of the AD group) to 1 (EEG features indistinguishable from the EEG features of the control group).

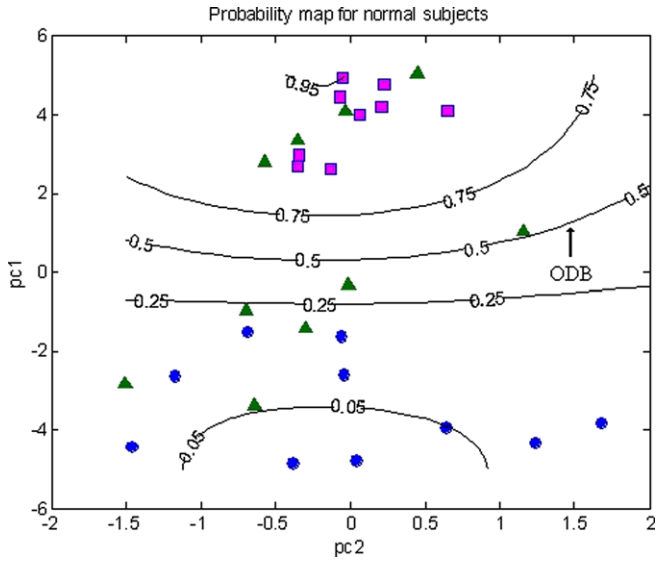

Fig. 3. The same two-dimensional representation of the results of the SPR analysis for the AD and control groups as in Fig. 2. The MCI group is added to the graph by treating their EEG recordings in the same manner and their corresponding coordinates shown in the figure as green triangles.

average MCI index value fell in between the average values for the AD and control groups and its standard deviation was considerably higher as evident by the distribution in Fig. 3. According to our methods, four of them could be said to belong to the control class and five to the AD class. One of the MCI individuals is too close to the ODB for the method to be able to determine the class accurately and is thus deemed to be of an indeterminate class.

The 10 MCI subjects have been followed up annually for 4 years and five of them progressed to AD, three of them within 12 months. The initial EEG pattern of those three subjects was not distinguishable from the pattern of the AD group. One MCI subject had progressed to AD at the 2 years control but his initial EEG pattern was indistinguishable from the controls'. However, at the time of the AD diagnosis this subject had substantial psychiatric symptoms (delusions) which might influence the quality of the clinical diagnosis. The fifth MCI patient had progressed to AD at the 4 year control. The EEG pattern of this MCI patient was originally more similar to AD (Fig. 4).

The AD patients usually attend a follow-up every 6 months. The control subjects that concluded the study were evaluated 2 years after their participation. No control had converted to AD but one control had subjective memory complaints after 4 years not confirmed by a relative and thus not fulfilling the criteria of MCI.

In order to evaluate the effects of scopolamine on the accuracy of our AD/control classification a comparison was made between a set of EEG feature pairs extracted from the EEG. Thus, instead of evaluating principal components, EEG feature pairs were used as the principal components in a two-dimensional classifier and the accuracy of the AD classification calculated for each pair using 10-fold cross validation (Duda et al., 2001). The feature pairs were composed of a selection of the features in Table 2 and to include the effects of scopolamine for comparison a ratio of each feature calculated before and after scopolamine administration was used as a single feature. To demonstrate the effect of scopolamine 13 features based on the typical frequency bands of the EEG were used from a single EEG channel, Cz. The two alpha bands and the two beta bands were combined into a single alpha band and beta band, respectively. Thus this set of features corresponds to the first 17 features in Table 2. The resulting histograms are shown in Fig. 5. There was an obvious shift to higher accuracy using the ratios instead of using only the EEG features before scopolamine administration.

4. Discussion

In this study, the use of EEG for the diagnosis of AD was evaluated. A very clear separation was demonstrated between 10 AD patients with mild or moderate disease and nine controls using the first two principal components based on the EEG features extracted from the data. It was not considered reliable to use more combinations of features, since the groups were small. The EEG patterns of the 10 MCI patients were heterogeneous as a group compared to the patterns of the AD and control groups. Three of those patients were diagnosed as having AD within 12 months and their individual EEG patterns had all been indistinguishable from those of the AD group at the time of the EEG recording as is evident in Fig. 4. This result indicates that this method might be helpful to distinguish those patients with MCI who develop AD in the following year from those who do not. This is in agreement with results of other researchers using different methods of analysing EEG. In a review published in 2008 (Jackson and Snyder, 2008), summarizing the literature of the last 6 years it was concluded that there were promising features in qEEG and event-related potentials that could serve as biomarkers for MCI and early AD. A project using spatial information content of resting EEG voltage by artificial neural network (ANN) correctly separated MCI from early AD in more than 92% of cases (Buscema et al., 2007). Researchers who previously applied EEG to classify MCI and AD subjects followed the MCI subjects for an average of 21 months and were able to predict progression with 85% accuracy by using only EEG features (Jelic et al., 2000). It has even been shown that EEG features can be used to predict which normals with self-reported cognitive decline will progress to MCI or dementia. Based on nine baseline variables it was possible in that study to distinguish between decliners and non-decliners during a 7 year follow-up period. Precision was even better when neuropsychological scores were added to the EEG

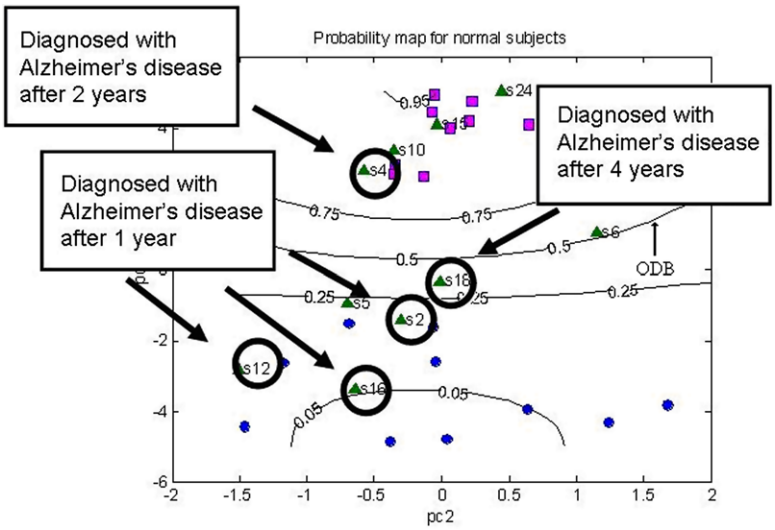

Fig. 4. Some of the MCI patients progressed to AD in the years following their participation in this study. Subjects 2, 12 and 16 were diagnosed with AD within 1 year of the trial. Subject 4 was diagnosed with AD after 2 years. Subject 18 was diagnosed with AD after 4 years.

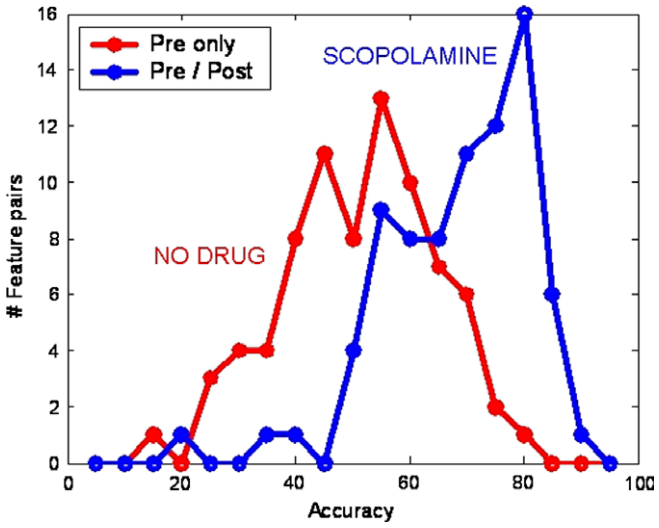

Fig. 5. Pattern recognition before and after administration of 0.3 mg scopolamine iv. The effects of scopolamine on diagnostic accuracy tested for a single EEG channel. For each EEG feature pair the diagnostic accuracy is calculated. The "NO DRUG" histogram on the left represents the accuracy of AD classification using the EEG features before scopolamine injection only and the "SCOPOLAMINE" histogram on the right represents the accuracy when using a ratio of features before scopolamine injection to after injection.

logistic regression (Prichep et al., 2006). A study where 69 MCI subjects were followed up for over 1 year showed that the 24 who converted to AD had different cortical connecticity (spectral coherence) from those who were stable (Rossini et al., 2006). The present approach is different from the above mentioned studies. Instead of making a prediction model based on knowing the end result, we compared an independent group of MCI subjects to groups of controls and AD patients. Because of the small size of our trial, it is not possible to say if our method can predict progression into AD within 1 year. When detecting the early stages of AD, the reliability of methods like neuroimaging and neuropsychology is a function of disease severity. As attempts are made to detect the disease at progressively earlier stages the risk of overlap with non-AD pathology and healthy aging increases (Nestor et al., 2004). This should hold for EEG too and therefore it is doubtful that our method can predict many years into the future which MCI patients will progress to AD.

Using scopolamine in conjunction with an EEG measurement results in a higher AD diagnostic accuracy when compared with an EEG measurement without scopolamine according to our findings. It is a problem, however, that giving scopolamine to angle-closure glaucoma patients or those at risk of developing angle-closure glaucoma is undesirable (Eskandar et al., 2005). Therefore, scopolamine should only be reserved for cases of uncertain EEG outcome.

In this pilot study we had strict inclusion and exclusion criteria and the results may not be replicable in other cohorts, e.g. patients older than 80 years and smokers. On the other hand, the fact that the method could be used to predict progression to AD in MCI patients implies that the method is somehow connected to AD pathology. Looking at the interspersed triangles in Fig. 4, our results further advance the argument of heterogeneity of MCI progression to dementia (Gauthier et al., 2006).

After the initial results of this trial, it was decided to establish a database of 1000 EEGs of various dementias as well as normal controls to try to develop the EEG further as a diagnostic tool for AD. Having more EEGs to work with gives the advantage of being able to use more combinations of features to make a separation model without overfitting.

Disclosure of commercial interests

Mentis Cura is a private research and development company developing EEG technique for diagnostic purposes. The first author is currently working part time for the company as well as in the Memory Clinic.

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References

Agnoli A, Martucci N, Manna V, Conti L, Fioravanti M. Effect of cholinergic and anitcholinergic drugs on short-term memory in Alzheimer's dementia: a neuropsychological and computerized electroenchephalographic study. Clin Neuropharmacol 1983;6:311–23.

Burg JP. Maximum entropy spectral analysis. PhD thesis. California, USA: Stanford University; 1975.
Buscema M, Rossini P, Babiloni C, Grossi E. The IFAST model, a novel parallel nonlinear EEG analysis technique, distinguishes mild cognitive impairment and Alzheimer's disease patients with high degree of accuracy. Artif Intell Med 2007;40:127–41.
Christensen H, Maltby N, Jorm AF, Creasey H, Broe GA. Cholinergic 'blockade' as a model of the cognitive deficits in Alzheimer's disease. Brain 1992;115:1681–99.
Coyle JT, Price DL, Delong MR. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 1983;219:1184–90.
Duda RO, Hart PE, Stork DG. Pattern classification. 2nd ed. New York, USA: John Wiley & Sons, Inc.; 2001.
Ebert U, Kirch W. Review – scopolamine model of dementia: electroencephalogram findings and cognitive performance. Eur J Clin Invest 1998;28:944–9.
Eskandar OS, Eckford SD, Whittaker KW. Treatment of overactive bladder (OBA) with anti-cholinergic drugs and the risk of glaucoma. J Obstet Gynaecol 2005;25:419–21.
Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" – a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.
Goedert M, Spillantini MG. A century of Alzheimer's disease. Science 2006;314:777–81.
Gudmundsson S, Runarsson TP, Sigurdsson S, Eiriksdottir G, Johnsen K. Reliability of quantitative EEG features. Clin Neurophysiol 2007;118:2162–71.
Jackson CE, Snyder PJ. Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. Alzheimers Dement 2008;4:S137–43.
Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 2000;21:533–40.
Jeong JS. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004;115:1490–505.
Johannesson GH, Gudmundsdottir IR, Helgason J, Ofeigsson BG, Hrafnkelsdottir K, Olafsson DR, et al. The initial effects of scopolamine on the electroencephalogram in healthy human subjects. In: IEEE EMBS 25th annual international conference; 2003.
Knopman DS, Boeve BF, Petersen RC. Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia. Mayo Clin Proc 2003;78:1290–308.
McKann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health & Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.
Nestor PJ, Scheltens P, Hodges JR. Advances in the early detection of Alzheimer's disease. Nat Rev Neurosci 2004:S34–41.
Neufeld MY, Rabey MJ, Parmet Y, Sifris P, Treves TA, Korczyn AD. Effects of a single intravenous dose of scopolamine on the quantitative EEG in Alzheimer's disease patients and age-matched controls. Electroencephalogr Clin Neurophysiol 1994;91:407–12.
Nobili L, Sannita WG. Cholinergic modulation, visual function and Alzheimer's disease. Vision Res 1997;37:3559–71.
Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.
Prichep LS, John ER, Ferris SH, Rausch L, Fang Z, Cancro R, et al. Prediction of longitudinal cognitive decline in normal elderly with subjective complaints using electrophysiological imaging. Neurobiol Aging 2006;27:471–81.
Reisberg B, Ferris SH, Deleon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiat 1982;139:1136–9.
Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, et al. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 2006;143:793–803.
Snædal J, Guðmundsson G, Jónsson JE, Jónsdóttir J. Faraldsfræðileg rannsókn á vitrænni getu aldraðra á tveimur aðskildum svæðum á Íslandi. Læknablaðið 1997;83:646–53.
Terry AV, Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 2003;306:821–7.
Tómasson K. Athugun á glöpum hjá öldruðum og áfengissjúklingum með auðveldu stöðluðu prófi borin saman við mat starfsfólks. Læknablaðið 1986;72:246–59.
Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–6.