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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.
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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

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