

CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE IS PREDICTED BY SOURCES AND COHERENCE OF BRAIN ELECTROENCEPHALOGRAPHY RHYTHMS

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Abstract—Objective. Can quantitative electroencephalography (EEG) predict the conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD)?

Methods. Sixty-nine subjects fulfilling criteria for MCI were enrolled; cortical connectivity (spectral coherence) and (low resolution brain electromagnetic tomography) sources of EEG rhythms (δ =2–4 Hz; θ =4–8 Hz; α 1=8–10.5 Hz; α 2=10.5–13 Hz; β 1=13–20 Hz; β 2=20–30 Hz; and γ =30–40) were evaluated at baseline (time of MCI diagnosis) and follow up (about 14 months later). At follow-up, 45 subjects were still MCI (MCI Stable) and 24 subjects were converted to AD (MCI Converted).

Results. At baseline, fronto-parietal midline coherence as well as δ (temporal), θ (parietal, occipital and temporal), and α 1 (central, parietal, occipital, temporal, limbic) sources were stronger in MCI Converted than stable subjects ($P<0.05$). Cox regression modeling showed low midline coherence and weak temporal source associated with 10% annual rate AD conversion, while this rate increased up to 40% and 60% when strong temporal δ source and high midline γ coherence were observed respectively.

Interpretation. Low-cost and diffuse computerized EEG techniques are able to statistically predict MCI to AD conversion. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: mild cognitive impairment, dementia, Alzheimer's disease, EEG, neurodegeneration, cognitive decline.

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Abbreviations: AD, Alzheimer's disease; CI, confidence interval; EEG, electroencephalogram; HR, hazard ratio; IAF, individual alpha frequency; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; MCI Converted, mild cognitive impairment subjects showing progression to clinically evident Alzheimer's disease; MCI Stable, mild cognitive impairment subjects remaining stable; MMSE, Mini Mental State Examination; Nold, normal elderly; rCBF, regional cerebral blood flow; ROI, region of interest; S.E., standard error.

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Mild cognitive impairment (MCI) is a state of the elderly brain intermediate between normal cognition and dementia, being mainly characterized by objective evidence of memory impairment not yet encompassing the definition of dementia (Petersen et al., 1995, 2001).

There is a growing consensus on the idea that MCI is a precursor of Alzheimer's disease (AD) (Scheltens et al., 2002) based on the high rate of progression from this state to AD (Petersen et al., 2001). Indeed, in normal aging population annual conversion rate to AD ranges from 0.17% to 3.86% (Petersen et al., 2001; Frisoni et al., 2004), while in MCI it is remarkably higher ranging between 6 and 40% in the different series (Petersen et al., 2001; Jack et al., 2005), while a significant percentage is not progressing into dementia at all (Petersen et al., 1995, 2001).

In order to plan optimal therapeutic, organizational and rehabilitative interventions for MCI, a reliable prognostic indicator on the likelihood of progression to dementia would be required. Along this line electroencephalogram (EEG) would be an ideal candidate to this issue, since it is a widely diffused, non-invasive and low-cost procedure.

A great deal of attention has been directed to electrophysiological substrate of AD and MCI, to evaluate the "transition" hypothesis of a linear progression from MCI to mild AD. In mild AD, EEG rhythms differ from normal elderly (Nold) and vascular dementia subjects, AD patients being characterized by excessive delta (0–4 Hz) and theta (4–7 Hz) rhythms, and a significant decrement of posterior alpha (8–12 Hz) and beta (13–30 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Babiloni et al., 2004a, 2006e,f,g; Prichep et al., 1994). These EEG abnormalities were associated with altered regional cerebral blood flow (rCBF)/metabolism and with global cognitive function as evaluated by Mini Mental State Examination (MMSE) (Sloan et al., 1995; Rodriguez et al., 1998; Jeong, 2004). Furthermore, parieto-temporal EEG rhythms and rCBF have been correlated with severity of AD as expressed by MMSE score (Rodriguez et al., 1998). Furthermore, a prominent decrease of EEG spectral coherence at the alpha band in AD has been reported (Jelic et al., 2000; Knott et al., 2000; Adler et al., 2003).

When compared with Nold subjects, MCI subjects have shown increase of theta (4–7 Hz) power (Zappoli et al., 1995; Jelic et al., 1996) as well as decrease of alpha power (Zappoli et al., 1995; Jelic et al., 1996; Huang et al., 2000). In line with the "transition" hypothesis, these EEG parameters have presented an intermediate magnitude in

MCI subjects with respect to those observed in Nold and dementia patients (Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000). Of note, it should be remarked that these results just regard the use of linear approaches, and that further advancements have been obtained with the use of non-linear approaches (for more details see relevant reviews Jeong, 2004; Pereda et al., 2005).

It has been recently evidenced that EEG theta power (3.5–7.5 Hz) is higher in MCI subjects who will convert to AD compared with MCI subjects who will not. Logistic regression provided an overall predictive accuracy of 90% between baseline EEG features and probability of future decline (Prichep et al., 2006). Furthermore, spectral EEG coherence has shown to contribute to the classification of AD from Nold (Adler et al., 2003) and the conversion of MCI subjects to AD (Jelic et al., 2000). However, relatively small patients samples and quite long follow-up epochs have been taken into account; moreover, localization of spectral EEG rhythms and cortico-cortical connectivity have never been previously jointly evaluated.

The aim of the present study was to investigate whether combined analysis of EEG power and coherence provides early and reliable discrimination of MCI subjects who will convert to AD after a relatively brief follow-up; results are extremely encouraging.

EXPERIMENTAL PROCEDURES

Subjects

Sixty-nine MCI subjects were enrolled. A group of fifty age/sex-matched Nold subjects was also recruited, in order to preliminarily confirm that MCI subjects presented the typical changes of the EEG rhythms. During a clinical follow-up of about 14 months 24 MCI subjects—from now designed *MCI Converted*—showed progression to a clinically evident AD (according with the NINCDS-ADRDA criteria; McKhann et al., 1984). Instead, 45 MCI subjects remained stable within that period (*MCI Stable*). Table 1 summarizes the demographic and clinical data of Nold, MCI Converted and MCI Stable subjects. Of note, benzodiazepines, antidepressant and/or antihypertensive drugs were withdrawn for about 24 h before the EEG recordings. None of the subjects received any cholinergic therapy.

Diagnostic criteria

Inclusion criteria for MCI aimed at selecting elderly persons with objective cognitive deficits, especially in the memory domain, who did not meet yet criteria for a diagnosis of dementia or AD (Petersen et al., 1995, 2001): i) objective memory impairment on neuropsychological evaluation, as defined by performances ≥ 1.5 standard deviation below the mean value of age- and education-matched controls for a test battery including Busckhe-Fuld and Memory Rey tests; ii) normal activities of daily living; and iii) clinical dementia rating score of 0.5. Exclusion criteria were: i) mild AD; ii) evidence of other concomitant dementia; iii) evidence of concomitant extrapyramidal symptoms; iv) clinical and indirect evidence of depression as revealed by Geriatric Depression Scale scores ≥ 13 ; v) other psychiatric diseases, epilepsy, drug addiction, and vi) current or previous uncontrolled systemic diseases or recent traumatic brain injuries.

EEG recordings

EEG were recorded in resting, awake subjects (eyes-closed; 5 min; 0.3–70 Hz bandpass; 256 Hz sampling rate) from 19 AgCl

Table 1. Demographic and neuropsychological database of Nold and MCI subjects

Characteristic	Nold	MCI Stable	MCI Converted
N	50	45	24
Age (y)	68.4 (± 0.2 SE)	70 (± 1.1 SE)	72.7 (± 1.1 SE)
Education (y)	9.2 (± 0.5 SE)	7.3 (± 0.6 SE)	9.7 (± 1.1 SE)
Gender (M/F)	22/28	16/29	12/12
I MMSE	28.4 (± 0.2 SE)	26.3 (± 0.3 SE)	25.7 (± 0.4 SE)
II MMSE	—	26.1 (± 0.3 SE)	21.7 (± 0.7 SE)
T2–T1 (mo)	—	14.3 (± 1 SE)	14.8 (± 0.9 SE)
Disease duration (mo)	—	21 (± 0.2 SE)	19.5 (± 2.7 SE)
Apoc $\epsilon 4$	—	36%	35%

MCI subjects were subdivided in two sub-groups: MCI Stable and MCI Converted during the follow-up period. Legend: T2–T1=for MCI Stable, the interval between the last clinical control confirming the permanence in MCI condition (T2) and the date of EEG recording (T1); T2–T1=for MCI Converted, interval (months) between the date of clinical control showing conversion to AD (T2) and the date of EEG recording (T1); I MMSE=MMSE at T1; II MMSE=MMSE at T2.

cup electrodes positioned on standardized scalp sites (International 10–20 System) in the research laboratories of three Italian AFaR Hospitals of Brescia (1) and Rome (2) (EEG machines: EBneuro (Firenze, Italy) and Micromed (Treviso, Italy) systems). To monitor eye movements, the electrooculogram (0.3–70 Hz bandpass) was simultaneously acquired. The EEG data were analyzed and fragmented off-line in 2 s consecutive epochs, those with ocular, muscular and other types of artifact being preliminarily identified and discarded by a computerized automatic procedure. Two independent experimenters visually confirmed the EEG segments accepted for further analysis. Even if the type of EEG recording was identical to the one routinely employed within the frame of a diagnostic procedure, since this was gathered in an experimental protocol, local institutional ethics committees approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the authors' institutional review board.

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed power density of EEG rhythms with 0.5 Hz frequency resolution. The following standard band frequencies were studied: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–40 Hz). These band frequencies were chosen according with previous relevant EEG studies on dementia (Leuchter et al., 1993; Jelic et al., 1996; Besthorn et al., 1997; Chiaramonti et al., 1997; Rodriguez et al., 1999a,b; Babiloni et al., 2004a, 2006d,e,f,g). That choice made the results of the present study directly comparable with those of previous field studies. Furthermore, sharing of a frequency bin by two contiguous bands is a widely accepted procedure (Leuchter et al., 1993; Cook and Leuchter, 1996; Jelic et al., 1996; Besthorn et al., 1997; Nobili et al., 1998; Pucci et al., 1997; Kolev et al., 2002; Holschneider et al., 1999). As an additional advantage, this fits the theoretical consideration that near EEG rhythms may overlap at their frequency borders (Klimesch, 1996, 1999; Klimesch et al., 1997, 1998; Babiloni et al., 2004b, c,d,e,f).

Choice of fixed EEG bands did not account for individual alpha frequency (IAF) peak, defined as the frequency associated with the strongest EEG power at the extended alpha range (Klimesch, 1999). However, this should not affect the results, since most of the subjects had IAF peaks within the alpha 1 band

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