MCI patients’ EEGs show group differences between those who progress and those who do not progress to AD

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Abstract

The theta/gamma and alpha3/alpha2 ratio were investigated as early markers for prognosticating of progression to dementia. 76 subjects with mild cognitive impairment (MCI) underwent EEG recording, MRI scans and neuropsychological (NPS) tests. After 3 years of follow-up, three subgroups were characterized as converters to Alzheimer’s disease (AD, \(N = 18\)), converters to non-AD dementia (\(N = 14\)) and non-converters (\(N = 44\)). The theta/gamma and alpha3/alpha2 ratio, performance on cognitive tests and hippocampal volume, as evaluated at the time of initial MCI diagnosis, were studied in the three groups. As expected, MCI to AD converters had the smallest mean hippocampal volume and poorest performance on verbal learning tests, whereas MCI to non-AD converters had poorest cognitive performance in non-verbal learning tests, abstract thinking, and letter fluency. Increased theta/gamma ratio was associated with conversion to both AD and non-AD dementia; increased alpha3/alpha2 ratio was only associated with conversion to AD.

Theta/gamma and alpha3/alpha2 ratio could be promising prognostic markers in MCI patients. In particular, the increase of high alpha frequency seems to be associated with conversion in AD. EEG markers allow a mean correct percentage of correct classification up to 88.3%. Future prospective studies are needed to evaluate the sensitivity and specificity of these measures for predicting an AD outcome.

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1. Introduction

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; Petersen and Negash, 2008).

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 (Portet et al., 2006). 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.

It has been recently evidenced that EEG theta power (3.5–7.5 Hz) is higher in MCI subjects who will convert to Alzheimer’s disease (AD) compared with MCI subjects who will not (Prichep et al., 2006). In an independent study of the same year it was showed that delta (temporal), theta (parietal, occipital and temporal), and alpha1 (central, parietal, occipital, temporal and limbic) sources were stronger in MCI converted in AD than in stable subjects and the risk of progression could be calculated on annual basis (Gauthier et al., 2006; Rossini et al., 2006). A recent study showed that converters MCI were differentiated from stable MCI subjects by a reduction of alpha power over posterior leads. Reduction of alpha power and mean frequency were significantly cor-
related with poorer cognitive performance in psychometric tests (Luckhaus et al., 2008). More recently, individual risk of progression to AD has been identified by using a supervised artificial network EEG analysis (Rossini et al., 2008).

Selective modifications of individual rhythms could be more related to behavioural paradigms such as stimulus onset and motor response (Canolty et al., 2006; Missonnier et al., 2007) as well as to various recording artifacts (Moretti et al., 2003). In contrast, when the ratio between frequencies is considered, the events of interest are features of the ongoing oscillatory activity itself. That is, frequency ratio refers to reciprocal dependence between distinct frequency bands of the ongoing EEG rather than dependence between the EEG and an external/internal events and/or undesired artifacts. For this reason it could be a useful tool in the analysis of rest EEG, together with the single frequency bands power analysis.

A large body of the literature has previously demonstrated that in subjects with cognitive decline is present an increase of theta relative power (Moretti et al., 2007a,b, 2009b), a decrease of gamma relative power (Stam et al., 2003; Moretti et al., 2009b) as well as an increase of high alpha as compared to low alpha band (Moretti et al., 2007b). On the whole theta/gamma ratio and alpha3/alpha2 ratio could be considered reliable EEG markers of cognitive decline.

As a working hypothesis, EEG markers like theta/gamma and alpha3/alpha2 power ratio could show different modifications in patients with MCI who convert in AD from patients who will not. In the present study the possibility of two EEG markers of cognitive decline (increase of theta/gamma and increase of alpha3/alpha2 relative power ratio) to predict conversion to AD was investigated in subjects with MCI, also characterized by hippocampal volume measures and neuropsychological (NPS) test scores.

2. Materials and methods

2.1. Subjects

For the present study, 76 subjects with MCI were recruited from the memory Clinic of the Scientific Institute for Research and Care (IRCCS) of Alzheimer’s and psychiatric diseases ‘Fatebenefratelli’ in Brescia, Italy. All experimental protocols had been approved by the local Ethics Committee. Informed consent was obtained from all participants or their caregivers, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Diagnostic criteria

Patients were taken from a prospective project on the natural history of MCI. The project was aimed to study the natural history of non-demented persons with apparently primary cognitive deficits, i.e., deficits not due to psychic (anxiety, depression, etc.) or physical (hypothyroidism, vit. B12 and folate deficiency, uncontrolled heart disease, uncontrolled diabetes, etc.) conditions. Patients were rated with a series of standardized diagnostic and severity instruments, including the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the Clinical Dementia Rating Scale (CDRS; Hughes et al., 1982), the Hachinski Ischemic Scale (HIS; Rosen et al., 1980) and the instrumental and basic activities of daily living (IADL, BADL, Lawton and Brodie, 1969). In addition, patients underwent diagnostic neuroimaging procedures (magnetic resonance imaging, MRI), and laboratory testing to rule out other causes of cognitive impairment. These inclusion and exclusion criteria for MCI were based on previous seminal studies (Petersen et al., 1995, 1997, 2001; Portet et al., 2006; Geroldi et al., 2006; Dubois et al., 2007). Inclusion criteria of the study were all of the following: (i) complaint by the patient, or report by a relative or the general practitioner, of memory or other cognitive disturbances; (ii) Mini-Mental State Examination score of 24–27/30, or MMSE of 28 and higher plus low performance (score of 2–6 or higher) on the clock drawing test (Lezak et al., 2004); (iii) sparing of instrumental and basic activities of daily living or functional impairment steadily due to causes other than cognitive impairment, such as physical impairments, sensory loss, gait or balance disturbances, etc. Exclusion criteria were any one of the following: (i) patients aged 90 years and older; (ii) history of depression or juvenile-onset psychosis; (iii) history or neurological signs of major stroke; (iv) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence; (v) use of psychoactive drugs, including acetylcholinesterase inhibitors or other drugs enhancing brain cognitive functions; and (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus), or traumatic brain injuries. All patients underwent: (i) semi-structured interview with the patient and – whenever possible – with another informant (usually, the patient’s spouse or a child of the patient) by a geriatrician or neurologist; (ii) physical and neurological examinations; (iii) performance-based tests of physical function, gait and balance; (iv) neuropsychological battery assessing memory (Babcock Story Recall – Rey–Osterrieth Complex Figure, Recall – Auditory-Verbal Learning Test, immediate and delayed recall; Lezak et al., 2004) verbal and non-verbal memory, attention and executive functions (Trail Making Test B, A and B–A; Inverted Motor Learning – Clock Drawing Test; Lezak et al., 2004), abstract reasoning thinking (Raven Colored Progressive Matrices; Lezak et al., 2004), frontal functions (Inverted Motor Learning); language (Phonological and Semantic fluency – Token test, Lezak et al., 2004), and apraxia and visuo-constructional abilities (Rey–Osterrieth Complex Figure, Rey figure copy, Clock Drawing Test; Lezak et al., 2004); (v) assessment of depressive symptoms by means of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). A more extensive battery would have been helpful in detecting early and more subtle deficits. Anyway, it should be considered that a larger battery is more time consuming and could bias the global level of attention in subjects with cognitive impairment. On the whole, we feel that the NPS battery was reliable to detect the threshold of conversion in dementia.
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