

Resting State Cortical EEG Rhythms in Alzheimer's Disease: towards EEG markers for clinical applications. A review.

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Abstract

Human brain contains an intricate network of about 100 billion neurons. Aging of the brain is characterized by a combination of synaptic pruning, loss of cortico-cortical connections and neuronal apoptosis that provoke an age-dependent decline of cognitive functions. Neural/synaptic redundancy and plastic remodeling of brain networking, also secondary to mental and physical training, promotes maintenance of brain activity and cognitive status in healthy elderly for everyday life. However, age is the main risk factor for neurodegenerative disorders such as Alzheimer's disease (AD) that impact on cognition. Growing evidence supports the idea that AD targets specific and functionally connected neuronal networks and that oscillatory electromagnetic brain activity might be a hallmark of the disease. In this line, digital electroencephalography (EEG) allows non-invasive analysis cortical neuronal synchronization as revealed by resting state brain rhythms. This review provides an overview of the studies on resting state eyes closed EEG rhythms recorded in amnesic mild cognitive impairment (MCI) and AD subjects. Several studies support the idea that spectral markers of these EEG rhythms such as power density, spectral coherence, and other quantitative features differ among normal elderly, MCI, and AD subjects, at least at group level. Regarding the classification of these subjects at individual level, most of the studies showed a moderate accuracy (70-80%) in the classification of EEG markers relative to normal and AD subjects. In conclusion, resting state EEG makers are promising for large-scale, low-cost, fully non-invasive screening of elderly subjects at risk of AD.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in geriatric patients, and is characterized by loss of intellectual (especially memory) and behavioral abilities that interfere with daily functioning. It tends to increase with age reaching 30% to 50% by the age of 85 (Vicioso, 2002; Graves and Kukull, 1994).

In the brain aging including prodromal AD, neural/synaptic redundancy and plastic remodeling of brain networking guarantees functional maintenance, so that neuronal death and synaptic loss can occur in the absence of cognitive symptoms for several years. These neuroprotective mechanisms are facilitated by mental and physical training, and constitute a sort of "cognitive or brain reserve".

The lack of objective cognitive impairment at the earlier stages of prodromal AD motivates the use of instrumental markers of AD in association to standard assessment of cognitive functions with "paper and pencil" neuropsychological batteries (Dubois et al., 2007). Some instrumental markers are already mature for clinical applications such as dosing of A beta amyloid and tau proteins in cerebrospinal fluid, magnetic resonance imaging (MRI) of hippocampus volume, and positron emission tomography (PET) of brain glucose metabolism/regional cerebral blood flow (rCBF) or PIB ligand (Wolf et al., 2003; Dubois et al., 2007). Of note, these markers are expensive, not available in any memory clinic, and/or partially invasive for a wide screening use in large populations of elderly subjects at risk of AD. In contrast, electroencephalographic (EEG) markers are cheap, largely available, and fully non-invasive, in line with ideal features of daily clinical routines (Rossini et al., 2007).

Standard EEG techniques are characterized by low spatial resolution (several centimeters) when compared to structural MRI and PET techniques producing relatively non-invasive views of "in vivo" brain anatomy (millimeters to few centimeters). However, structural MRI does not provide functional information about brain, and PET scan of brain

glucose metabolism/rCBF is limited in its temporal resolution (i.e. seconds to minutes for PET) compared to EEG (i.e. milliseconds; Rossini et al., 2004). It should be noted that high temporal resolution of EEG is crucial for the study of an emerging property of brain activity, namely the spontaneous and event-related oscillatory gross electromagnetic activity at different frequencies ranging at 1-4 Hz (delta), 4-8 Hz (theta), 8-13 Hz (alpha), 13-30 Hz (beta), and >30 Hz (gamma). Any EEG frequency band conveys peculiar physiological information on brain functional state during sleep and wake periods (Nunez, 1999).

In recent years, great attention has been focused on the evaluation of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as clinical markers of the early stages of AD (Celesia et al., 1987, Rossini et al., 2007, 2009, Vecchio and Määttä, 2011, Yener et al., 2008, 2009). In this regard, the recording of resting state eyes closed cortical EEG rhythms represents a fully standardized procedure very easy and rapid to be carried out in clinical environment. In contrast to ERPs, the use of resting state EEG rhythms does not require stimulation devices or registration of subject's behavior, and is not prone to fatigue and anxiety typically associated to task performance. This is ideal when EEG recordings are performed in elderly subjects. Furthermore, resting state cortical EEG rhythms can be recorded in highly comparable experimental conditions in normal subjects, individuals with subjective memory complaints, objective mild objective cognitive impairment (MCI), and overt AD (Rossini et al., 2007).

The following review of the field literature outlines the impact of resting state eyes closed EEG markers for the instrumental assessment of AD. Its major goal is to highlight the emerging neurophysiological findings to determine whether markers derived by resting state eyes closed EEG rhythms provide potentially useful information as candidate markers for clinical applications in individual AD patients (i.e. early diagnosis, prognosis, and disease monitoring).

2. Resting state eyes closed cortical EEG rhythms along physiological aging and AD

Comparison of resting state EEG power among AD and control groups

Resting state eyes closed cortical EEG rhythms typically change across physiological aging, with gradual modifications visible as variation of EEG power density spectrum computed at scalp electrodes or in mathematically estimated cortical sources (Rossini et al., 2007). The following bulk of studies addressed these EEG changes at group level. Compared to healthy young subjects, healthy elderly subjects were characterized by a marked decrease of alpha power (8–13 Hz) (Dujardin et al., 1994, 1995; Klass and Brenner, 1995; Klimesch, 1999). Such changes in alpha power were confirmed in a large sample of healthy subjects (N = 215, 18–85 years) showing an age-dependent power decrement of posterior low-frequency alpha (alpha 1; 8–10.5 Hz) and delta rhythms across physiological aging (Babiloni et al., 2006a). The present results complement several study showing a shift of alpha activity toward frontal brain regions in resting state EEG of Alzheimer patients (Dierks et al., 1993) as well as during cognitive processes in physiological aging (Yordanova et al., 1996, 1998, Kolev et al., 2002, Başar et al., 2010). Noteworthy, parieto-occipital alpha rhythms presumably reflect the dominant oscillatory activity of brain networks in the resting state eyes closed condition, as a result of a massive synchronization of cortical pyramidal neurons (Pfurtscheller and Lopes da Silva, 1999). This activity is modulated by thalamo–cortical and cortico–cortical interactions facilitating/inhibiting the transmission of sensorimotor information and the retrieval of semantic information from cortical storage (Steriade and Llinas, 1988; Brunia, 1999; Pfurtscheller and Lopes da Silva, 1999). In the condition of wake resting state, low-frequency alpha rhythms (about 8-10 Hz) can be observed in widely distribute brain networks, and reflect the general brain arousal and subject's global attentional readiness (Klimesch, 1996, Klimesch et al., 1997, Klimesch et al., 1998, Rossini et al., 1991;

Steriade and Llinas, 1988). Power of these rhythms also reflect intelligent quotient, memory, and global cognition status (Klimesch, 1999). In parallel, high-frequency alpha rhythms (about 10-12 Hz) reflect the oscillation of more selective neural systems for the elaboration of sensorimotor or semantic information (Klass and Brenner, 1995; Klimesch, 1996, 1997). Of note, it is be remarked that the topology related frequencies should be carefully taken into account; the differentiation of 8-10 Hz, 10-12 Hz is not an overall phenomenon and can be completely different in anterior and posterior areas as reflects in several experiments in both humans and animals (Başar et al., 2010, Schürmann et al., 2000).

At group level, resting state eyes closed cortical EEG rhythms present topographical and frequency differences in the EEG power spectra of healthy normal elderly (Nold), MCI, cerebrovascular dementia (CVD), Parkinson disease with dementia (PDD), and AD subjects. When compared to Nold subjects, AD subjects showed a power increase of topographically widespread delta and theta rhythms and a power decrease of posterior alpha (8–13 Hz) and/or beta (13–30 Hz) rhythms (Babiloni et al., 2004a; Dierks et al., 2000; Huang et al. 2000; Ponomareva et al., 2003; Jeong, 2004; Prichep, 2005). Posterior alpha rhythms were lower in power in AD than CVD and PDD subjects, whereas topographically widespread theta rhythms were higher in power in CVD and PDD than AD subjects (Babiloni et al., 2004a, 2011a).

Resting state EEG power density differed between AD patients and amnesic MCI subjects which were considered to be at high risk to suffer of prodromal. There was an “intermediate” power of low-frequency alpha rhythms (8–10.5 Hz) in parietal and occipital regions in MCI compared to mild AD and Nold subjects (Babiloni et al., 2006b). Furthermore, maximum of alpha and beta power shifted more anteriorly in AD patients compared to Nold and MCI subjects (Huang et al., 2000). Moreover, longitudinal studies have shown that increased delta or theta power, decreased alpha and beta power, and slowing

of EEG mean frequency predicted in some way the progression from MCI to dementia at about 1-year follow up (Huang et al., 2000; Jelic et al., 1996, 2000; Grunwald et al., 2001; Kwak, 2006; Rossini et al., 2006). High power of posterior alpha rhythms also predicted a stable global cognitive function in MCI subjects at 1-year follow up (Babiloni et al 2010a).

Some EEG studies assessed changes in the resting state eyes closed EEG rhythms along the disease progression, namely along the period from “baseline” to “follow up” at about 1-year follow up or longer. In MCI subjects, the EEG markers of disease progression included a power increase of theta and delta rhythms in temporal and occipital regions as well as a power decrease of beta rhythms in temporal and occipital regions (Jelic et al, 2000). AD patients were characterized by a power increase of parieto-occipital theta and delta rhythms as well as by a power reduction of alpha and beta rhythms in parieto-occipital regions (Coben et al., 1985). Furthermore, AD patients showed a power increase of theta and delta rhythms in temporal-occipital regions (Soininen et al. 1989,1991).

Relationships of resting state EEG rhythms with markers of neurodegeneration and global cognitive status in Nold, MCI, and AD subjects

Resting state eyes closed EEG rhythms were found to be related to objective markers of neurodegeneration in AD subjects as revealed by rCBF or glucose hypometabolism. An early study showed the first evidence of a relationship among autopsy findings, visual features of resting state EEG rhythms, and rCBF in AD subjects. AD subjects were characterized by fronto-temporal cortical degeneration and parietal/temporal loss of neurons, visual EEG abnormalities, and reduction of parietal rCBF as revealed by intra-arterial-133-Xenon clearance technique (Jóhannesson et al., 1977). A bulk of subsequent studies compared power of resting state eyes closed EEG rhythms and SPECT perfusion (^{99m}Tc

HMPAO) in AD subjects. It was shown that AD subjects were correctly classified on the basis of an association among clinical diagnosis, rating of resting state EEG rhythms, and rCBF (Sloan et al., 1995). In AD subjects, a global decrease in rCBF was associated with a shift on the topographical maximum alpha power in the posterior direction; in addition, alpha and beta power were positively correlated to cognitive status as measured by Syndrome-Kurz test, whereas delta and theta power inversely correlated with MMSE score (Müller et al., 1997). Further evidence showed that topographically widespread delta and theta power, lower alpha power, and lower alpha peak frequency characterized AD patients compared to control subjects, while SPECT perfusion was reduced in all regions with special emphasis in temporal and parietal areas (Passero et al., 1995). Moreover, there was a close relationship between rCBF and certain quantitative EEG parameters in AD patients, mainly the power of theta and delta rhythms (Passero et al., 1995). In AD patients, widely distributed delta and alpha power were also correlated with the SPECT perfusion level in the parietal regions, the delta power being also correlated with the SPECT perfusion level in right hippocampus (Rodriguez et al., 1999). Based on these SPECT and EEG variables, 88% of AD subjects (sensitivity) and 89% of Nold subjects (specificity) were correctly classified (Rodriguez et al., 1998). A correlation was also observed between parieto-occipital alpha power and SPECT perfusion in early AD subjects, namely lower power of parieto-occipital alpha rhythms was related to lower rCBF in temporal and parietal regions (Claus et al., 2000). Compared to frontal lobe dementia patients, AD subjects were denoted by more severe EEG abnormalities, less severe reduction of frontal rCBF, and more severe reduction of parietal rCBF as revealed by SPECT perfusion (Julin et al., 1995). The above SPECT findings were corroborated by PET evidence showing a reduced parieto-temporal hypometabolism, increased widely distributed delta and theta power, and reduced parieto-temporal alpha power

(Buchan et al., 1997). Consistent localization of PET brain hypometabolism and abnormal power of EEG rhythms was confirmed by further investigations in AD patients (Dierks et al., 2000). There was also a significant negative correlation between a slow to fast EEG activity ratio indexing the degree of slowing of the EEG rhythms and the regional metabolic rate for oxygen in parietal and temporal regions (Buchan et al., 1997).

A relationship between the power of resting state eyes closed EEG rhythms and rCBF or brain glucose hypometabolism of neurodegeneration also emerged by studies testing the effects of pharmacological treatments in AD subjects. Beneficial effects of estrogen on female AD patients (6 weeks) were observed as increase of SPECT perfusion level in right frontal regions, decrement of delta and theta power in bilateral frontal regions, and improved dementia rating score (Ohkura et al., 1994). Citicoline (i.e. an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine) was given for 2-weeks period of treatment vs. 2-weeks period of placebo in AD patients with the important genetic risk factor of dementia called epsilon 4 allele of the APOE (Alvarez et al., 1999). There was an increase of the cerebrovascular function as revealed by transcranial Doppler in association with an increase of occipital alpha power and a topographically widespread decrease of delta power, especially in left temporal regions (Alvarez et al. 1999). On the other hand, the effects of AcetylCholinesterase inhibitors such as tetrahydroaminoacridine and donepezil were tested. A medium-term period of tetrahydroaminoacridine (6 weeks) therapy showed different clinical effects in the recruited AD patients, the responders to the therapy being characterized by pre-treatment rCBF and increased post-treatment beta power (Minthon et al., 1993). A long-term period of donepezil in AD patients (about 1 year) showed a small area of SPECT perfusion increase in right occipital cuneus and left lingual gyrus but no remarkable change of EEG power associated to rCBF (Rodriguez et al., 2004). In addition, a correlation was observed between the mean frequency of EEG power and rCBF in posterior

parietal cortex regardless the effects of the therapy (Rodriguez et al., 2004). As an innovative therapeutic approach, AD patients received a continuous deep electrical stimulation for 12 months of memory circuits including entorhinal areas, hippocampus, fornix, and hypothalamus with no serious adverse events (Laxton et al., 2010). PET scans showed an early and striking reversal of the impaired glucose utilization in temporal and parietal regions that was maintained after 12 months of continuous deep brain stimulation, while MMSE score suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients. Changes in cortical EEG rhythms were also mapped.

Power of resting state eyes closed EEG rhythms was correlated to brain atrophy in the typical track of AD neurodegeneration as revealed by structural MRI. In AD patients with global cognitive impairment, hippocampal atrophy was associated to increased power of delta and theta rhythms in temporal and parietal regions (Helkala et al., 1996), in line with recent magnetoencephalographic evidence (Fernandez et al., 2003). Furthermore, volume of hippocampus was related to decreased power of alpha rhythms in temporal, parietal, and occipital regions in MCI and AD subjects (Babiloni et al., 2009a). The same was true for the relationship between the power of resting state eyes closed EEG rhythms and volumetric changes of sub-cortical white (i.e. connection pathways to and from the cerebral cortex) and cortical grey matter. The total amount of volume of frontal white matter was positively correlated to the frontal delta power in AD patients; namely, the higher the white matter volume, the lower the (pathological) delta power thus suggesting that reduced modulation/regulatory inputs to frontal cortex through white matter might dis-inhibit the intrinsic delta oscillations of cerebral cortex (Babiloni et al., 2006g). Furthermore, global delta and alpha power was related to the total amount of atrophy of cortical grey matter in amnesic MCI and AD subjects as revealed by MRI voxel-to-voxel volumetry of lobar brain volume; the higher the total grey matter volume, the lower the global delta power, the higher

the global alpha power (Babiloni et al., 2011b). Of note, these modifications of delta and alpha power in MCI and AD subjects were not merely due to vascular brain lesions of white matter (Babiloni et al. 2008a,c, Babiloni et al., 2011c). Keeping in mind the above findings, it can be speculated that posterior delta/theta and alpha power of resting state eyes closed EEG rhythms reflect neurodegenerative processes along the time course of AD, at least at group level.

Power of resting state eyes closed EEG rhythms was repeatedly found to be correlated to subjects' cognitive status in MCI and AD subjects. It has been shown that posterior alpha power was correlated to global cognitive status as measured by ADAS-cog in MCI and AD subjects; namely the lower the alpha power, the lower the cognitive status (Luckhaus et al., 2008). This relationship can be extended to cognitive health condition. Furthermore, posterior delta and alpha power were correlated to MMSE score in Nold, MCI and AD subjects; namely, the lower the alpha power, the higher the delta power, the lower the cognitive status (Babiloni et al., 2006b). Moreover, lower cognitive performance as revealed by CAMCOG scores was associated with lower alpha power in parieto-occipital and fronto-central regions in AD subjects (Claus et al., 2000).

These findings suggest that EEG markers at delta and alpha rhythms may be used alone or in combination with structural MRI, SPECT, and PET markers to corroborate and support the standard clinical and neuropsychological assessment of MCI and AD subjects. In this line, a first important study has combined EEG, structural MRI, and PET markers using an ensemble of classifiers based decision fusion approach, in order to determine whether a strategic combination of these different modalities can improve the diagnostic accuracy over any of the individual data sources when used with an automated classifier (Polikar et al. 2010). Results showed an improvement of up to 10%-20% using this approach compared to the classification performance obtained when using each individual data source (Polikar et al.

2010).

Longitudinal studies on resting state EEG rhythms in AD subjects

Few longitudinal studies have evaluated resting state eyes closed EEG rhythms to determine the changes in the baseline EEG markers that may be able to predict a cognitive decline at follow up. It has been shown that in MCI subjects, the markers of disease progression included an increase in the power of theta and delta activity in the temporal and occipital lobes as well as the reduction of beta power in the temporal and occipital lobes (Jelic et al., 2000). AD patients were characterized by an increase in the power of theta and delta activity and by the reduction of alpha and beta activity in the parieto-occipital lobes (Coben et al., 1985). Furthermore, half of the AD patients showed an increase in the power of theta and delta activity in a temporal-occipital lead (Soininen et al., 1989).

Functional coupling of resting state EEG rhythms in Nold, MCI, and AD subjects

Above results on resting state eyes closed EEG power and neuroimaging of the structural and functional brain organization in MCI and AD subjects have led to the widely supported hypothesis that neuronal networks of temporally coordinated brain activity across different regional brain structures underpin cognitive function and denote AD neurodegeneration. In this vein, failure of integration within a network may lead to cognitive dysfunction in prodromal and manifest AD. In this sense, AD can be viewed at least in part as a disconnection syndrome (Bokde et al., 2009). In this theoretical framework, EEG power spectrum per se does might not fully capture the impairment of functional neural connectivity. Promising markers of functional neural connectivity derive from the

measurement of the functional coupling of resting state eyes closed EEG rhythms between pairs of electrodes. Linear components of such coupling, functional co-ordination, and mutual information exchange can be evaluated by the analysis of spectral coherence (Gerloff et al., 1998; Gevins et al., 1998; Thatcher et al., 1986; Rappelsberger and Petsche, 1988). Spectral coherence is a normalized value that quantifies the temporal synchronization of two EEG time series between pairs of electrodes in the frequency domain and can be derived by fast fourier transform -FFT- (Rappelsberger and Petsche 1988; Pfurtscheller and Andrew 1999). Its basic theoretical assumption is that when the oscillatory activity of two cortical areas is functionally coordinated, the EEG rhythms of these cortical areas show linear correlation and high spectral coherence. In general, decreased coherence reflects reduced linear functional coupling and information transfer (i.e., functional uncoupling or unbinding following) among cortical areas or the reduced modulation of common areas by a third region. In contrast, an increase of the coherence values is interpreted as an enhancement of the linear functional connections and information transfer (i.e., functional coupling or binding), which reflects the interaction of different cortical structures for a given task. Indeed, it has been repeatedly demonstrated that perceptive, cognitive, and motor processes are associated with enhanced EEG spectral coherence in the cortical regions involved in intensive task-related information processing (Sauseng et al., 2005; Babiloni et al., 2006c; Vecchio et al., 2007, 2010, 2011), as a function of the extension and type of the neural networks engaged (Pfurtscheller and Lopes da Silva, 1999; von Stein and Sarnthein, 2000). In addition, spectral coherence may reflect the integrity of cortical neural pathways (Locatelli et al., 1998).

At group level, functional coupling of resting state, eyes closed cortical EEG rhythms differs among Nold, MCI, and AD subjects. A bulk of previous EEG studies have reported a prominent decrease of coherence at alpha rhythms in AD compared to Nold subjects (Cook and Leuchter, 1996; Jelic et al., 1997; Almkvist et al., 2001; Locatelli et al., 1998; Wada et

al., 1998a,b; Knott et al., 2000; Adler et al., 2003; Leuchter et al., 1987, 1992; Jelic et al., 2000). This effect has been found to be associated with ApoE genetic risk, which is hypothesized to be mediated by cholinergic deficit (Jelic et al., 1997). On the other hand, previous studies have shown contradictory results with either a decrease or an increase of low-band EEG coherence at delta and theta rhythms (Locatelli et al., 1998; Adler et al., 2003, Leuchter et al., 1987; Brunovsky et al., 2003). A recent study has reconciled these conflicting results computing “total coherence” as obtained averaging the EEG spectral coherence across all combinations of electrode pairs (Babiloni et al., 2010b). The latter may better take into account frequency band-by-frequency band the global impairment of brain networks and cognition along the AD process, which is supposed to be a disease affecting the functional integration within cerebral neural networks supporting cognition. In such recent study, delta total coherence was higher in AD than MCI subjects and in MCI than Nold subjects (Babiloni et al., 2010b). Furthermore, the low-frequency alpha total coherence was lower in AD than in MCI and Nold subjects. Of note, these EEG coherence values were negatively correlated to (moderate to high) cholinergic lesion across the MCI subjects (Babiloni et al., 2010b). Non published data of our group indicated that spectral delta coherence was higher in the AD than MCI and Nold subjects, while spectral alpha coherence was lower in the AD than MCI and Nold subjects.

Spectral coherence is a linear measurement of the functional coupling of EEG rhythm. Instead, the so called ‘synchronization likelihood’ is an index capturing both linear and non-linear dimensions of this coupling. It has been shown that compared with the Nold subjects, patients with vascular dementia and mild AD presented a marked reduction of synchronization likelihood at both fronto-parietal (delta-alpha) and inter-hemispherical (delta-beta) electrode pairs (Babiloni et al., 2004b). The feature distinguishing the patients with mild AD with respect to patients with VaD groups was a more prominent reduction of

synchronization likelihood at fronto-parietal alpha rhythms, suggesting that mild AD is characterized by an abnormal fronto-parietal coupling of the dominant human alpha rhythms (Babiloni et al, 2004b). Furthermore, synchronization likelihood was lower in MCI than Nold subjects and in AD than MCI subjects at midline and right fronto-parietal electrodes (Babiloni et al., 2006c). The same was true for the likelihood of delta synchronization at the right fronto-parietal electrodes. For these EEG bands, the synchronization likelihood correlated with global cognitive status as measured by the mini mental state evaluation state (MMSE).

Spectral coherence and synchronization likelihood do not allow the determination of the directional flux of information in the fronto-parietal coupling of resting state EEG rhythms. This dimension can be explored by a technique called direct transfer function (DTF; Kaminski and Blinowska, 1991; Blinowska et al., 2010; Blinowska, 2011; Blinowska and Zygierewicz, 2011; Brzezicka et al., 2011). DTF has been proven to be reliable for the determination of directional information flux within linear EEG functional coupling, as an intrinsic feature of cerebral functional connectivity (Kaminski et al., 1997; Korzeniewska et al., 1997). In Kaminski et al., 1997 it was reported that in the resting state, eyes closed the EEG activity propagates mainly from posterior regions. This findings may be a reference point for assessment of changes in propagation for demented patients.

Across pathological aging, it has been shown that a reduction of parietal-to-frontal directional information flux within the functional coupling of alpha and beta rhythms is stronger in normal controls than in MCI and/or AD subjects (Babiloni et al., 2009b), in line with the idea of a common pathophysiological background linking these subjects at least at group level (Babiloni et al., 2009b, Vecchio and Babiloni, 2011). Noteworthy, such a direction of the fronto-parietal functional coupling is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by extent of white-matter

vascular disease supporting the additive model according to which MCI state would result from the combination of cerebrovascular and neurodegenerative lesions (Babiloni et al., 2008c).

3. Resting state eyes closed cortical EEG rhythms along physiological aging and AD: classification of MCI and AD individuals based on EEG markers towards clinical applications

In the previous section, the review of the literature shows that at group level, MCI and AD subjects are characterized by abnormal power of delta/theta and alpha rhythms in temporal, parietal, and occipital regions as well as by abnormal fronto-parietal coupling of these rhythms. In this section, we revise resting state eyes closed EEG studies testing the hypothesis that features of resting state eyes closed EEG studies can be used to classify single individuals towards diagnostic and prognostic clinical applications.

Concerning the classification of Nold, MCI, and AD subjects, it has been shown that spectral EEG coherence and other EEG features contributed to the discrimination of Nold from mild AD with 89–45% of success, from MCI to AD with 92–78% of success, and the conversion of MCI subjects to AD with 87–60% of success (Huang et al., 2000; Adler et al., 2003; Jelic et al., 2000; Nuwer, 1997; Claus et al., 1999; Bennys et al., 2001; Brassens et al., 2004; Lehmann et al., 2007; Missonnier et al., 2006; Buscema et al., 2007).

Concerning the progression from MCI to AD status, it has been shown that a multiple logistic regression of theta power (3.5–7.5 Hz), mean frequency, and inter-hemispheric coherence was able to predict the decline from MCI to AD at long term with an overall predictive accuracy of about 90% (Prichep et al., 2006). Furthermore, spectral coherence and power of EEG rhythms in 69 MCI cases were evaluated at baseline and at a follow up after 14 months (Rossini et al., 2006). At follow-up, 45 subjects were classified as stable MCI

(MCI Stable), whereas the remaining 24 subjects converted to AD (MCI “converted”). Results showed that at baseline, fronto-parietal midline coherence as well as delta (temporal), theta (parietal, occipital and temporal), and low-frequency alpha (central, parietal, occipital, temporal, limbic) power were stronger in MCI “converted” than MCI “stable” subjects (Rossini et al., 2006). Cox regression modeling showed low midline coherence and weak temporal source was associated with 10% annual rate AD conversion, while this rate increased up to 40% and 60% when strong temporal delta source and high midline gamma coherence were observed, respectively (Rossini et al., 2006). This outcome indicated that resting state EEG markers can contribute to the prediction of the progression from MCI to AD at about 1-year follow up.

These findings encourage confirmatory studies aimed at testing prognostic and perhaps diagnostic value of resting state eyes closed EEG markers. These confirmatory studies are mandatory due to the great variability of the EEG variables and classifiers used in the mentioned investigations. In the mentioned studies, EEG variables for the classification purposes were the simple voltage of on-going resting state eyes closed EEG spatial distributions used as an input to artificial neural networks (Buscema et al., 2007; Rossini et al., 2008). Alternatively, they were derived from linear spectral procedures such as power density and coherence spectra used as inputs to linear and non-linear classifiers (Gueguen et al., 1991; Szeliés et al., 1992; Rodriguez et al., 1998; Huang et al., 2000; Ihl et al., 2000; Bennys et al., 2001; Adler et al., 2003; Rossini et al., 2006; Abásolo et al., 2008; Knyazeva et al., 2010; Ahmadlou et al., 2011). In other cases, the input EEG variables were obtained by non-linear procedures typically inspired by chaos theory (Pritchard et al., 1994).

4. Conclusions

Keeping in mind the present review of the literature, it can be concluded that resting

state eyes closed cortical delta/theta and alpha rhythms as indexed by posterior source power, fronto-parietal coherence and DTF were abnormal in amnesic MCI and AD subjects, at least at group level. These EEG markers may reflect an abnormal synchronization of cortical pyramidal neurons and a functional disconnection among cortical areas along AD process. Indeed, power and local functional coupling of delta and theta rhythms reflect a cortical disconnection from sub-cortical structures, while power and local functional coupling of alpha rhythms reflect an effective global synchronization of default cortical networks in the wake resting state eyes closed condition (Spiegel et al., 2006).

The present review of the literature also showed encouraging results unveiling an interesting moderate accuracy around 70-80% (on average) in the classification of individual EEG datasets in MCI and AD subjects, although a variety of methodologies were applied. This accuracy level may be useful for the preliminary screening of large populations of elderly subjects at risk of AD such as subjects with subjective memory impairment or people with genetic risk of AD. Furthermore, the resting state eyes closed EEG markers may be used alone or in combination with structural MRI, SPECT, and PET markers to corroborate and support the standard clinical and neuropsychological assessment of MCI and AD subjects in the diagnostic process. Each of these approaches has shown some promising outcomes, however, a comprehensive data fusion analysis should be performed to investigate whether these different modalities carry out complementary information. If affirmative, they can be combined to provide a more accurate analysis taking into account important variables such as costs, invasiveness, and availability of the procedures in the territory.

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