Biomarkers in Alzheimer’s disease with a special emphasis on event-related oscillatory responses

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ABSTRACT

Alzheimer’s disease (AD) is a devastating neurodegenerative dementing illness. Early diagnosis at the prodromal stage is an important topic of current research. Significant advances were recently made in the validation process of several biomarkers, including structural/amyloid imaging, cerebrospinal fluid measurements, and glucose positron emission tomography. Nevertheless, there remains a need to develop an efficient, low cost, potentially portable, noninvasive biomarker in the diagnosis, course, or treatment of AD. There is also a great need for a biomarker that would reflect functional brain dynamic changes within a very short time period, such as milliseconds, to provide information about cognitive deficits. Electrophysiological methods have the highest time resolution for reflecting brain dynamics in cognitive impairments. There are several strategies available for measuring cognitive changes, including spontaneous electroencephalography (EEG), sensory-evoked oscillations (SEOs), and event-related oscillations (EROs). The term “sensory-evoked” (SE) implies responses elicited upon simple sensory stimulation, whereas “event-related” (ER) indicates responses elicited upon a cognitive task, generally an oddball paradigm. Further selective connectivity deficit in sensory or cognitive networks is reflected by coherence measurements. When simple sensory stimulus is used, a sensory network becomes activated, whereas an oddball task initiates an activation in a sensory network and additionally in a related cognitive network.

In AD, spontaneous activity reveals a topographically changed pattern of oscillations. In addition, the most common finding in spontaneous EEG of AD is decrease of fast and increase of slow frequencies. The hyperexcitability of motor and sensory cortices in AD has been demonstrated in many studies. The motor cortex hyperexcitability has been shown by transcranial magnetic stimulation studies. Also, the SEOs reflecting sensory network indicate a visual sensory cortex hyperexcitability in AD, as demonstrated by increased responses over posterior regions of the hemispheres. On the other hand, ERO studies reflecting activation of a cognitive network imply decreased responses in fronto-central regions of the brain in delta and theta frequencies. Coherence studies show the connectivity between different parts of the brain. Studies of SE coherence in mild AD subjects imply almost intact connectivity in all frequency ranges, whereas ER coherence is decreased in wide connections in alpha, theta, and delta frequency ranges. Moreover, alpha ER coherence seems to be sensitive to cholinergic treatment in AD.

In further research in a search of AD biomarkers, multimodal methods should be introduced to electrophysiology in order to validate these methods. Standardization and harmonization of user-friendly acquisition and analysis protocols in larger cohort populations are also needed in order to incorporate electrophysiology as a part of the clinical criteria of AD.

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16.1. Introduction

As the most common cause of dementias, Alzheimer’s disease (AD) is one of the most intensively researched subjects in neuroscience. In this paper, we review and investigate possible electrophysiological biomarkers in AD. The status of many biomarker techniques is reviewed, focusing on brain oscillatory responses in AD.

This paper is outlined as follows. We start by reviewing: (1) signal processing methods to detect perturbations in brain dynamics; (2) changes of spontaneous EEG and event-related (ER) potentials in AD; (3) the major effects of AD on brain sensory-evoked (SE) or event-related oscillatory (ERO) responses and their changes in AD subjects on cholinergic medication; (4) perturbations in synchrony: (a) SE coherences and (b) ER coherences in AD. In previous studies of spontaneous electroencephalography (EEG), AD patients had increased delta and theta, and decreased alpha rhythms compared to healthy controls and/or amnesic mild cognitive impairment (MCI) subjects (Dierks et al., 2000; Huang et al., 2000; Jelic et al., 2000; Jeong, 2004; Babiloni et al., 2006a, 2010). For a review of spontaneous EEG and/or ERP, the reader is referred to Rossini et al. (2007), Jackson and Snyder (2008), Lizio et al. (2011), Vecchio et al. (2013, in this issue). For a review of evoked/ER oscillations, see Başar-Eroğlu et al. (2001), Başar and Güntekin (2008), Başar et al., (2010), Dauwels et al. (2010a,b), Güntekin and Başar, (2010), Yener and Başar, (2010, 2013, in this issue). The reader is also referred to many studies on the spontaneous EEG by Babiloni et al. At the end of this paper, we offer some concluding remarks.

AD is the most common and devastating cause of degenerative dementias and is generally found in people aged over 65. Approximately 24 million people worldwide have dementia, of which two-thirds are due to AD (Ferri et al., 2005). Clinical signs of AD are characterized by progressive cognitive deterioration, together with declining activities in daily life, and by neuropsychiatric symptoms. Although the ultimate cause of AD is unknown, genetic factors are clearly indicated, as dominant mutations in three different genes have been identified (Waldemar et al., 2007). Diagnosis of MCI and AD is important for several reasons. Diagnosis gives the patients and their caregivers time to make decisions related to life and to plan for the future. Early diagnosis of AD allows the use of medications when they are most useful and reduces the cost of the disease, it also delays institutionalization, and electrophysiological biomarkers may be used in early diagnosis (Dauwels et al., 2010a,b).

Neuropathological characteristics of AD are intracellular neurofibrillary tangles due to accumulation of phosphorylated tau protein and extracellular amyloid plaque due to amyloid beta (Aβ) deposition. The commonly used NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV-TR (American Psychiatric Association, 2000) criteria for AD assessments detect AD at a relatively late stage of the disease. The pathological process of AD is thought prior to eventual diagnosis of AD dementia. This long “preclinical” phase of AD would provide a critical opportunity for therapeutic intervention; however, there is a need to elucidate the link between the pathological cascade of AD and the emergence of clinical symptoms (Sperling et al., 2011). This notion calls for the definition of procedures for early diagnosis/prognosis of AD in the preclinical condition called MCI (Petersen et al., 2001) or very early phase of AD. In the majority of cases, amnestic MCI is a precursor of AD with an annual conversion rate of approximately 15% per year (Petersen et al., 2001; Rasquin et al., 2005; Alexopoulos et al., 2006) that may be predicted from hippocampal
atrophy rates in magnetic resonance images (Jack et al., 2005). Furthermore, the pathological deposits in AD may affect certain oscillatory networks; as Adaya-Villanueva et al. (2010) demonstrated, kainate-induced beta-like hippocampal network activity is differentially affected by amyloid β1–42 and relatively shorter and soluble peptide amyloid β25–35. However, it remains unclear which particular evoked oscillatory activity is sensitive to amyloid deposition.

Although it is very important to have reliable and validated markers for MCI-to-AD progression or for MCI/AD diagnosis, these are not yet available (McKhann et al., 2011). Potential biomarkers should be noninvasive, inexpensive, and potentially portable in order to screen large population samples of elderly subjects at risk of AD.

The National Institute on Aging and the Alzheimer’s Association convened an international workgroup to review the biomarker, epidemiological, and neuropsychological evidence, and to develop recommendations to determine the factors that best predict the risk of progression from “normal” cognition to MCI and AD dementia. A conceptual framework and operational research criteria were recommended to test and refine these models with longitudinal clinical research studies. These recommendations are only intended for research purposes and do not have any clinical implications at this time (Sperling et al., 2011).

The National Institute on Aging worked on Molecular and Biochemical Markers of Alzheimer’s Disease (1998) stated that “the ideal biomarker... should detect a fundamental feature of the neuropathology and be validated in neuropathologically confirmed cases; it should have a sensitivity of >80% for detecting AD and a specificity of >80% for distinguishing other dementias; it should be reliable, non-invasive, simple to perform, and inexpensive” (Wright et al., 2009).

The global cost of dementia in 2005 was estimated to be over 300 billion USD per year (Wimo et al., 2006). As there is a rise in age-specific incidence of dementia (Matthews et al., 2006) and aging global population, a biomarker for dementia becomes a central topic for brain research.

Medical diagnosis of AD can be easily dismissed even by specialist centers at a rate of 10–15% (Knopman, 2001). Diagnosis is usually made by extensive neuropsychological testing, the results of which depend on many heterogeneous social and cultural factors. As aging is the most
important risk factor for development of dementia, the rapidly aging populations, especially in developing countries (Keskinoğlu et al., 2006) within recent decades, cause AD to become an important public health problem. There is increasing evidence implying that pathological development of AD starts several decades before the appearance of clinical symptoms (Price and Morris, 1999). Interventions to pathological course, as early as possible, may be more effective than at any other time period.

For these reasons, there is an increasing need for a biomarker derived from blood tests, spinal fluid, imaging or neurophysiological techniques.

16.2.1. Imaging

16.2.1.1. Structural magnetic resonance imaging

Until recently, the role of imaging was the exclusion of other pathologies, including hydrocephalus, vascular infarcts or lacunes, or tumors. Recently, the use of specialized magnetic resonance imaging (MRI) methods allows pathologies to be determined. For example, new microbleeds that are indicative of amyloid deposits on a vascular bed are caught by susceptibility-weighted images in MRI, or the hyperintensities of putamen, cortex, or pulvinar in diffusion-weighted images can be used in diagnosis of Jakob–Creutzfeldt disease (Vitali et al., 2011). Patterns of atrophy also offer important clues about several degenerative pathologies. Semantic dementia can be diagnosed by severe asymmetrical anterior temporal atrophy on T1-weighted coronal images, indicating ubiquitin-positive, tau-negative neuronal inclusions; a behavioral variant FTD is characterized by bifrontal severe atrophy (Rabinovici and Miller, 2010), and primary progressive aphasia is characterized by left perisylvian atrophy (Yener et al., 2010). Recent publications offer a wealth of evidence that the presence of hippocampal atrophy, detectable either by visual assessment or by volumetric measurement, is proportional to the severity of the disease (Jack et al., 2011a,b) and furthermore it can predict the conversion from MCI to AD (De Carli et al., 2007). Even visual rating of one coronal slice of MRI for differentiating MCI from controls showed
sensitivity and specificity rates of 80% and 85% (Duara et al., 2008). In the light of these neuroimaging findings, the new diagnostic criteria for AD propose to incorporate the presence of temporal lobe atrophy.

16.2.1.2. Single photon emission tomography

Single photon emission tomography (SPECT) measures regional blood flow, whereas fluorodeoxyglucose positron emission tomography (FDG-PET) examines glucose metabolism in the brain. The deficit pattern in posterior cingulate, posterior precuneus and temporal lobe regions helps to differentiate AD from controls with a sensitivity and specificity rate of 90% and 70%, respectively (Jagust et al., 2007).

Neurotransmitters can also be traced by neuroimaging techniques. Dopamine transport loss in SPECT provided good separation between dementia with Lewy body (DLB) and AD. Transporter loss in DBLS was of similar magnitude to that seen in Parkinson’s disease. The significant reductions in transporter loss binding occurred in the caudate and anterior and posterior putamens in subjects with DLB compared with subjects with AD and controls (O’Brien et al., 2004).

16.2.1.3. Fluorodeoxyglucose positron emission tomography

Substantial impairment of FDG uptake in temporo-parietal association cortices in PET emerges as a predictor of rapid progression to dementia in MCI patients. Frontal and temporo-parietal metabolic impairment is closely related to disease progression in longitudinal studies, and multicenter studies suggest its utility as an outcome parameter to increase the efficiency of therapeutic trials (Herholz, 2010), in a study comparing hypometabolic convergence index (HCl) in FDG-PET for the assessment of AD to other biological, cognitive, and clinical measures, and it shows potential as a predictor of clinical decline in (MCI) patients. HCIs were significantly different in the probable AD, MCI converter, MCI stable and normal control groups and were correlated with clinical disease severity. MCI patients with either higher HCIs or smaller hippocampal volumes had the highest hazard ratios (HRs) for an 18 month progression to probable AD (7.38 and 6.34, respectively), and those who both had an even higher HR (36.72; Chen et al., 2011). In another study comparing CSF, MRI, and PET, all biomarkers were found sensitive to a diagnostic group. Combining MR morphometry and CSF biomarkers improved diagnostic classification (controls vs. AD). For MRI, hippocampal volume, entorial and retrosplenial thickness yielded an overall classification accuracy of 85.0%. For FDG-PET, entorial, retrosplenial, and lateral orbitofrontal metabolism gave an overall classification accuracy of 82.5. For CSF, the ratio of total tau protein T-tau/amyloid β42 peptide (Aβ42) as the single unique predictor produces an overall classification accuracy of 81.2%. In the final model, when hippocampal volume, retrosplenial thickness, and T-tau/Aβ42-ratio were included as predictors, an overall classification accuracy of 88.8% was achieved (Walhovd et al., 2010). MR morphometry and PET were largely overlapping in value for discrimination, as also shown by Karow et al. (2010). The only study using multimodal ERO responses, MRI and PET data fusion comes from Polikar et al. (2010) who included 37 AD and 36 healthy elderly subjects. The accuracy rates when the top 15 classifiers were used were 80% for ERO+MRI, 81% for ERO+PET, 80% for MRI+PET, and 86% for ERO+MRI+PET.

16.2.1.4. Pittsburgh compound-B positron emission tomography

One of the current favorable explanations for AD pathogenesis is the amyloid cascade hypothesis. According to this hypothesis, accumulation of toxic amyloid beta peptides initiates AD pathogenesis, which in turn results in the formation of phospho-tau (P-tau) filaments (Hardy and Selkoe, 2002). Amyloid imaging has improved our understanding of timing in the pathological process. C-labeled Pittsburgh compound-B (PIB) PET
allows amyloid deposits to become evident in vivo one to two decades before the symptoms appear. This became complicated when nondemented elderly subjects were reported to display amyloid burden. However, recent publications report that high amyloid burden is a risk for progression to dementia (Mathis et al., 2005; Villemagne et al., 2008). Amyloid burden does not correlate with glucose metabolism in AD, yet it is congruent with CSF amyloid by 91% (Jagust et al., 2009). However, it still shows an increasing level among normal controls, MCI or AD subjects (Quigley et al., 2011). In another study using a combination of three methods (MRI, FDG-PET, and CSF) for classifying AD from healthy controls, a classification accuracy of 93.2% (with a sensitivity of 93% and a specificity of 93.3%), and only 86.5% were achieved when using even the best individual modality of biomarkers. Similarly, in classifying MCI from healthy controls, a classification accuracy of 76.4% (with a sensitivity of 81.8% and a specificity of 66%) for the combined method, and 72% using the best individual modality of biomarkers were found. Further analysis on MCI sensitivity of the combined method indicated that 91.5% of MCI converters and 73.4% of MCI nonconverters were correctly classified. In that study, the most discriminative markers were MR and FDG-PET features (Zhang et al., 2011).

Future preventive studies of at-risk populations will address many fundamental questions by means of multimodal use of these techniques.

16.2.2. Cerebrospinal fluid and plasma biomarkers

As today, the core diagnostic cerebrospinal fluid (CSF) markers for AD are Aβ42, T-tau, and P-tau. Low levels of Aβ42 together with high levels of either P- or T-tau identify AD with a sensitivity and specificity rate of over 80% (Blennow et al., 2010). Various laboratories have developed cut-off criteria for defining the “low” Aβ42 and “high” tau from autopsy series or large cohorts (Mattsson et al., 2009; Shaw et al., 2009; Visser et al., 2009). The lower level of Aβ42 is explained by the deposition of the peptide in plaques in AD. Beta-secretase (BACE-1) activity in CSF is increased in AD and MCI patients that are often considered as prodromal AD by many. CSF Aβ42 and tau are quite stable over time and are therefore not considered as valuable markers for progression (Blennow et al., 2007). However, a later report states that a reduction in the CSF Aβ42 level denotes a pathophysiological process that significantly departs from normality (i.e., becomes dynamic) early, whereas the CSF total tau level and the adjusted hippocampal volume are biomarkers of downstream pathophysiological processes. The CSF total tau level becomes dynamic before the adjusted hippocampal volume, but the hippocampal volume is more dynamic in the clinically symptomatic MCI and AD dementia phases of the disease than is the CSF total tau level (Jack et al., 2011b). In MCI subjects, the combination of greater learning impairment and increased atrophy are associated with highest risk (hazard ratio of 29.0): 85% of patients with both risk factors converted to AD within 3 years versus 5% of those with neither. The presence of medial temporal atrophy was associated with shortest median dementia-free survival (15 months) (Heister et al., 2011).

Recent quantitative multiplex proteomics approach to identify AD achieved a diagnostic accuracy of 90% and 81% over a 7-year follow-up for AD and MCI, respectively (Ray et al., 2007). However, later reports repeating these tests in larger series yielded lower accuracy (Soares et al., 2009).

16.2.3. Genetic biomarkers

The amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN 2) are currently accepted as susceptibility genes for early onset AD. Sortilin-related receptor (SORL1) is involved in trafficking APP from the cell surface to the Golgi–endoplasmic reticulum complex (Reitz and Mayeux, 2009). Underexpression of SORL1 leads
to overexpression of Aβ42 and an increased risk of AD (Rogaeva, 2007). Besides the well-known risk increase in ApoE4 allele carriers in late onset AD (Hyman et al., 1996), urokinase-type plasminogen activator (PLAU) gene (Ertekin-Taner et al., 2005) and insulin degrading enzyme mapping (Ertekin-Taner et al., 2004) were found to be related to Aβ42 levels.

Despite promising developments in imaging and CSF biomarkers, there are limitations to their widespread use. PET technologies are not widely available and involve high cost. Collection of CSF is not common in many centers for the diagnosis of dementia and is also an invasive method. The accessibility of MRI is good in many countries; however, the lack of standard algorithms currently limits its applicability as a biomarker. There is a great need for low-cost and noninvasive screening. We suggest a set of candidate electrophysiological biomarkers for AD. Table 1 illustrates the current possible biomarkers for AD.

16.3. Signal processing methods

Spontaneous EEG is routinely used in clinical applications, mostly for epilepsy. Within the past 30 years, it was also used in understanding cognition or related brain dynamics. Electroencephalography or ER potentials are proposed by several authors as possible biomarkers in AD (for reviews, see Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2006; Jackson and Snyder, 2008; Başar et al., 2010; Lizio et al., 2011). However, the full potential of electrophysiological methods in helping to predict (Cichocki et al., 2005; Rossini et al., 2006), to diagnose (Yener et al., 1996; Polich and Herbst, 2000; Jeong, 2004; Babiloni et al., 2006a; Karrasch et al., 2006), and to monitor either treatment or progress (Jelic et al., 2000; Babiloni et al., 2006b) in AD patients has not been incorporated into routine clinical practice. The term “event-related” refers to a potential elicited after an event including a cognitive task. The word “evoked” is used when the potential is elicited by simple sensory stimulation. The term “oscillations” imply rhythm of specific time interval. EROs in various frequency bands may reflect different aspects of information processing (Başar, 1980, 2004).

In this paper, we review recent progress in investigating AD using methods such as EEG, event-related potential (ERP), and derived oscillatory responses. Studies have shown that AD-related changes in EEG (Rossini et al., 2006, 2007), ERP, or brain oscillatory responses (for a review, see Başar et al., 2010; Yener and Başar, 2010) can be summarized as: (1) slowing of the spontaneous EEG; (2) reductions in amplitude or increase in latency of ERP; (3) reductions in amplitude or phase-locking of ERO activity in slow frequency ranges over fronto-central regions; (4) amplitude increments of visual sensory-evoked oscillatory (SEO) activities over primary sensory cortical regions; (5) reductions in EEG or ERO synchrony, such as (a) conspicuous decrement of ER coherences (i.e., elicited upon a cognitive task) between frontal and all other parts of the brain in many frequency ranges; and (b) less prominent SE coherence (i.e., elicited upon simple sensory stimuli) decrement between frontal and modality-specific primary sensory cortical regions.

Those perturbations, however, are not always detectable on an individual basis, as there tends to be large variability among AD patients. This finding implies that none of these methods alone is currently suitable as a biomarker for early AD or MCI. However, many recent studies have investigated how to improve the sensitivity of EEG or brain oscillatory responses to understand brain dynamics in AD. The changes observed in this disorder may also provide clues to understanding the healthy brain. This paper reviews the progress reported in such studies.

16.3.1. Spontaneous EEG

To date, many signal-processing techniques were utilized to reveal pathological changes in spontaneous EEG associated with AD (Jeong, 2004). A number of studies have been published related
to the analysis of oscillatory dynamics in MCI and AD patients, and several groups have published core results on EEG rhythms in MCI patients (see Vecchio et al., in this issue). EEG is one of the tools widely used in functional brain studies due to its high temporal resolution and low cost. Previous EEG studies have shown an increased power of low frequencies (delta (0.5–4 Hz) and theta (4–8 Hz) bands) and decreased power of high frequencies (alpha (8–13 Hz) and beta (15–30 Hz) bands) over posterior regions in AD patients compared with healthy subjects (Yener et al., 1996; Bethsorn et al., 1997; Van der Hiele et al., 2007; Bhattacharya et al., 2011) and related to cognitive profile (Smits et al., 2011). Generally the “slowing” of the EEG rhythms has been correlated with severity of dementia. In particular, significant decrease of cortical alpha\textsubscript{1} (8–10.5 Hz) power in central, parietal, temporal, and limbic areas is observed in AD patients (Babiloni et al., 2004). However, the age of AD onset seems to change this benchmark. Early onset AD subjects more often display focal or diffuse EEG abnormalities than those with late onset (De Waal et al., 2011). Patients with amnestic MCI (aMCI) have also shown reduction of alpha\textsubscript{1} band power in parieto-occipital and temporal areas. The evaluation of the LORETA solutions indicates a correlation with hippocampal volumes in the MCI/AD spectrum (Babiloni et al., 2009a). In MCI subjects, the EEG markers of disease progression included a power increase of theta and delta rhythms in temporal and occipital regions and a power decrease of beta rhythms in temporal and occipital regions (Soininen et al., 1991; Jelic et al., 2000) or power decrease of alpha rhythms in temporal–occipital regions (Coben et al., 1985). An entropy study reported irregular magnetoencephalographic (MEG) activity among AD patients and a significantly higher variability than controls. The method achieved both specificity and sensitivity rates of 85% (Poza et al., 2008). Lehmann et al. (2007) compared resting EEG in 116 mild AD cases with 45 elderly controls and reported sensitivity and specificity of 85% and 78%, respectively.

Osipova et al. (2005) also reported a shift of alpha from parieto-occipital regions to temporal regions in AD. Recent studies found that frontal delta and occipital theta sources of amnesic MCI patients were greater than those of healthy controls (Babiloni et al., 2010). A negative correlation was also found between frontal delta sources with global cognitive status (MMSE) and the volume of frontal white matter (Babiloni et al., 2006c). Furthermore, increased power of delta and theta activity in temporal and parietal regions (Helkala et al., 1996) and decreased alpha power in temporal, parietal, and occipital regions were associated with hippocampal atrophy (Babiloni et al., 2009a). Thus, spontaneous EEG rhythm abnormalities observed

### Table 1

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AD: Alzheimer’s disease; FDG-PET: fluorodeoxyglucose positron emission tomography; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.
in MCI and AD patients might reflect the pathology of cortical information processing within distributed cortical networks. It is speculated that alterations of spontaneous EEG rhythms are affected in MCI and AD patients (Babiloni et al., 2009b) and AD patients (Yener et al., 1996), mainly due to the loss of cholinergic basal forebrain neurons projecting to the hippocampus and fronto-parietal connections. Furthermore, spontaneous EEG has been suggested as a useful predictive technique in patients with MCI who will later develop AD (Cichocki et al., 2005). A longitudinal study evaluated the baseline EEG markers for predicting a cognitive decline at follow-up. However, Osipova et al. (2006) did not find any difference between MEG activity of MCI subjects and controls in resting state. Another meta-analysis of resting EEG has indicated that classification accuracies between AD and controls ranged between 2.3 and 38.5, and diagnostic odds ratios consequently showed large variations between 7 and 219 (Jelic and Kowalski, 2009). The best results distinguishing between MCI stable and MCI/AD achieved up to 86% sensitivity by using a computational model compressing the temporal sequence of EEG data into spatial invariants (Buscema et al., 2010). Despite the wealth of published research and reported high indexes of diagnostic accuracy of EEG in individual studies, evidence of diagnostic utility of resting EEG in dementia and MCI is still not sufficient to establish this method for routine initial clinical evaluation of subjects with cognitive impairment. In that sense, temporal summation of EEG responses after stimulation is expected to give more accurate results in evaluation of AD (Polich and Herbst, 2000).

16.3.2. Motor-evoked potentials

An earlier pathology study indicated relatively spared primary sensory or motor areas in AD (Braak et al., 1993). A transcranial magnetic stimulation (TMS) study found reduced TMS-evoked P30 in AD over ipsilateral temporo-parietal areas, and contralateral fronto-central cortex corresponding to the sensorimotor network, and decrease in the N100 amplitude in the MCI subjects when compared with the control subjects (Julkunen et al., 2008). Ferreri et al. (2003) showed that motor cortex excitability was increased in AD, and the center of gravity of motor cortical output, as represented by excitable scalp sites, showed a frontal and medial shift. This finding may indicate a functional reorganization, possibly after the neuronal loss in motor areas. The authors concluded that hyperexcitability might be caused by a disregulation of the intracortical GABAergic inhibitory circuitries and selective alteration of glutamatergic neurotransmission, and the method might supplement traditional methods to assess the effects of therapy. The hyperexcitability in motor areas, as shown by Ferreri et al. (2003), is congruent with the findings of hyperexcitable visual sensory areas in mild AD subjects as shown by Yener et al. (2009). In their study, simple SEO responses resulted in increased theta responses over parietal and occipital regions where primary and secondary visual areas were located, whereas cognitive tasks elicited decreased theta phase-locking and delta responses over fronto-central regions. Decreased cortico-cortical connectivity between frontal and parieto-occipital areas has also been demonstrated by means of diminished coherence (Başar et al., 2010). Therefore, brain oscillatory responses indicate a decreased modulation of frontal lobes on the posterior parts of the brain where sensory visual cortices are located, possibly resulting in an increased response upon a simple sensory stimulation in AD.

16.3.3. P300 or event-related potentials

The target response of the applied P300 oddball paradigm is considered to be activated by four basic cognitive functions: “perception,” “focused attention,” “learning,” and “working memory” (Başar-Eroğlu and Başar, 1991; Halgren et al., 2002; Rektor et al., 2004; Klimesch et al., 2006). These potentials are obtained after averaging EEG after application of a cognitive task in a
time-locked and phase-locked way. The basic P300 is elicited by the oddball paradigm (Hillyard and Kutas, 1983), where rare “target” stimuli are randomly embedded in a sequence of standard stimuli. The P300 is named after a positive voltage maximum at about 300 ms response to the oddball stimulus. An oddball discrimination paradigm involves responding to stimuli that are dissimilar to the majority of stimuli presented. The subject is instructed to count target stimuli mentally. By means of this paradigm, subjects have to first perceive and then compare the stimuli with the one they were taught, to decide whether the stimulus is a target or not and, finally, to keep a mental count of the total number of target stimuli. These processes involve activation of many intriguing cognitive networks that last about 1 s, starting at about 50 ms, and peaking within the first 600-ms time window. Polich (1997) showed that the P300 of healthy subjects is affected by many factors including age and sex. The scalp topographic distribution of P300 amplitude was affected by the group factor, such that AD produced appreciably less frontal-to-parietal increase across task difficulty. P300 latency was relatively unaffected by scalp topography other than the usual increase from the frontal-to-parietal electrodes. Thus, at the group level, P300 can discriminate between AD and healthy controls (Rossini et al., 2006).

In recent years, studies have shown increase in P300 latency (Lai et al., 2010) and N200 latency (Missonnier et al., 2007) and decrease in N200 amplitude (Papaliagkas et al., 2008) in MCI or AD. Increase in P300 correlated with baseline cognitive scores (Papaliagkas et al., 2011a), and MCI subjects who progressed to AD had significantly lower Aβ42 levels (Papaliagkas et al., 2009), significantly higher N200 latencies and their P300 latency correlated with age (Papaliagkas et al., 2011b). Similar changes were also reported in somatosensory modality (Stephen et al., 2010). In patients with MCI with abnormal/reduced N400 or P600, word repetition effects had an 87–88% likelihood of dementia within 3 years (Olichney et al., 2008).

Genetically, AD mutation carriers without dementia showed less positivity in frontal regions and more positivity in occipital regions, compared to controls. These differences were more pronounced during the 200–300 ms period. Discriminant analysis at this time interval showed promising sensitivity (72.7%) and specificity (81.8%) (Quiroz et al., 2011). Another study on familial AD mutation carriers found significantly longer latencies of the N100, P200, N200, and P300 components, and smaller slow wave amplitudes (Golob et al., 2009). In another study comparing symptomatic carriers with asymptomatic carriers and noncarriers, the asymptomatic and noncarrier groups showed similar N400 amplitudes, whereas those of symptomatic carriers were significantly lower. However, N400 topography differed in mutation carrier groups with respect to the noncarriers. Intracranial source analysis evidenced that the presymptomatic carriers presented a decrease of N400 generator strength in right inferior-temporal and medial cingulate areas and increased generator strength in the left hippocampus and parahippocampus compared to the noncarrier controls (Bobes et al., 2010). Bennys et al. (2007) used prolonged P300 and N200 latencies to differentiate AD, MCI, and controls. The sensitivity rates were 87–95% for the differentiation of AD patients from MCI and control subjects, using prolonged P3 latencies (specificity 90–95%), whereas sensitivity when using N2 prolonged latencies was 70–75% (specificity 70–90%). Moreover, in the MCI group, N200 latencies strongly differentiated MCI from control subjects, with 90% sensitivity and 70% specificity; and correctly categorized 80% of MCI subjects against 73% for P300. In a visual pattern and motion onset EPs study, AD pathology in visual cortex was predicted (Fernandez et al., 2007). Ahiskali et al. (2009) introduced an approach using an ensemble of classifiers to combine ERP obtained from different electrode locations in the early diagnosis of AD.
It seems that late rather than earlier cognitive components in P300 show decreased amplitude, as reported by many groups, to differentiate between normal aging and AD (Polich and Corey-Bloom, 2005) by an accuracy rate of 92% (Chapman et al., 2007). ERPs have important predictive power in measuring conversion from MCI to AD (Missonnier et al., 2005, 2007; Olichney et al., 2008, 2011) by an accuracy rate of 79% (Chapman et al., 2011). In a study comparing AD and dementia with Lewy bodies, P300 latency was found to be delayed and its amplitude was lower with a different topography in DLB compared to AD groups (Bonanni et al., 2010).

16.3.4. Sensory evoked and event-related oscillations

The analysis of working memory has been one of major subjects of the major studies in neurophysiology. In the last few years, analysis of the oddball-P300 paradigm has become one the most commonly used methods in this context. Its underlying assumption is that the ERP response is evoked by the cognitive task (i.e., oddball paradigm in most cases), and can then be detected by averaging. The evoked responses increase the signal-to-noise ratio (SNR) in the average signal reflecting cognitive processes (Tallon-Baudry and Bertrand, 1999). EROs are elicited by digital filtering of “event-related potential” or “P300” in certain frequency bands, such as delta, theta, alpha, beta, and gamma. ERO responses can provide additional information about sensory and cognitive functions during stimulus and task evaluation (Başar, 1992; Başar et al., 1997). The first studies of brain oscillatory dynamics in P300 included those of Başar et al. (1984), Başar and Stamper (1985), Stamper and Başar (1985), Başar-Eroğlu et al. (1992, 2001), and Schürmann et al. (2001). Another series of studies on local oscillatory dynamics showed that the major operating rhythms of P300 are mainly the delta and theta oscillations (Başar-Eroğlu et al., 1992; Kolev et al., 1997; Demiralp et al., 1999; Spencer and Polich, 1999; Karakaş et al., 2000; Yordanova et al., 2000; Başar et al., 2001). The prolongation of theta, delta, and alpha oscillations was described for the target stimuli in comparison to standard stimuli (Stamper and Başar, 1985; Başar-Eroğlu et al., 1992; Yordanova and Kolev, 1998; Demiralp and Ademoğlu, 2001; Öiniz and Başar, 2009). The methods described in the referenced studies were mainly amplitude and latency measures of averaged filtered responses, spectral power of target response, wavelet decomposition, and phase-locking factor of target and nontarget responses.

16.3.4.1. Sensory evoked oscillatory SEO responses

SEO responses can be elicited upon application of simple sensory stimuli without any cognitive load by digital filtering of “evoked potential” in certain frequency bands. Interpretation of differing cognitive and sensory networks might be possible by comparing the SEO responses with ERO responses upon application of a cognitive task. Haupt et al. (2008) studied visual evoked oscillatory responses in AD, MCI, and healthy controls. They found dominant gamma and beta 2 bands in elderly controls in all significantly different brain areas. In addition, MCI and AD subjects differed from controls in current density distribution with a movement from the right hemisphere toward the left hemisphere in AD/MCI.

In a visual SEO study (Yener et al., 2009), it was shown that, when a stimulus does not contain a cognitive load, the differences between AD and healthy control groups were not as prominent as those observed for cognitive tasks. Furthermore, contra-intuitively, parieto-occipital theta-evoked oscillations were higher in untreated AD subjects than both controls and treated AD groups. This finding, showing a hyperexcitable visual sensory cortex, is congruent with a TMS study by Ferreri et al. (2003), indicating hyperexcitable motor cortex in AD. This is an understandable result, since the neuropathological changes at the mild stage of AD do not involve the primary sensory or motor areas (Fig. 2, Braak et al., 1993; Yener et al., 2009).
Osipova et al. (2006) analyzed 40 Hz auditory steady-state responses in AD patients. They showed that the amplitudes were significantly increased in AD compared to controls. Another steady-state-evoked study by Van Deursen et al. (2011) indicated a significant increase of 40 Hz (in gamma frequency range) SSR power in the AD group compared to MCI and controls. Furthermore a moderate correlation between 40 Hz SSR power and cognitive performance was shown, as measured by ADAS-cog. During early visual processing, Haupt et al. (2008) showed topological differences between AD patients and healthy controls upon application of LORETA analysis and increased beta2 and gamma power in AD. The results of Osipova et al. (2006), Haupt et al. (2008), Yener et al. (2009), and Van Deursen et al. (2011) showed that SEOs were higher in AD subjects upon application of sensory stimuli. This could be due to the lack of frontal modulation on sensory cortical areas in AD patients. Earlier work of Sauseng et al. (2005) indicated the control of posterior cortical activation by anterior brain areas. An increase of prefrontal EEG alpha amplitudes, which is accompanied by a decrease at posterior sites, may thus not be interpreted in terms of idling or “global” inhibition but may enable a tight functional coupling between prefrontal cortical areas and, thereby, allows the control of the execution of processes in primary visual brain regions. As Yener and Başar (2010) stated, decreased inhibition of cortical visual sensory processing, possibly due to decreased prefrontal activity, may lead to increased SE cortical responses in AD (Fig. 2).

16.3.4.2. ERO responses
Event-related synchronization is elicited by EEG recording during a cognitive task. It gives an induced response that is time-locked, but not phase-locked. The major change seen in spontaneous EEG of AD is “slowing” over posterior hemispheres (Vecchio et al., in this issue). Missonnier et al. (2006a,b) conducted a longitudinal study and analyzed ERS in MCI patients upon application of N-back working memory task. Their results showed that progressive MCI subjects demonstrated lower theta synchronization in comparison to stable MCI subjects with a sensitivity rate of 87% and a specificity rate of 60%. The same group’s longitudinal study on progressive and stable MCI subjects during the N-back task showed that progressive MCI cases displayed significantly higher gamma fractal dimension values compared
to stable MCI cases (Missonnier et al., 2010). A similar increase in gamma band was also found by Van Deursen et al. (2008, 2011). Also, EEG functional coupling for alpha and beta rhythms was stronger in normal elderly than in MCI and/or AD patients (Karrasch et al., 2006). In an event-related synchronization (ERS) study, MCI and control subjects were examined longitudinally by an N-back paradigm (Deiber et al., 2009). In that study, induced theta response described as time-locked, but not phase-locked, activity was decreased over frontal regions in MCI. The results demonstrated that an early decrease of induced theta amplitude occurs in progressive MCI cases; in contrast, induced theta amplitude in stable MCI cases did not differ from elderly controls. Deiber et al. (2007) compared the results of working memory tasks to passive tasks and showed that induced frontal theta activity was related to focused attention to the stimulus. Global theta activity during a visual cognitive task, on the other hand, did not differ between healthy controls and progressive or stable MCI groups. The authors stated that primary cortical processing of visual stimulus was not affected in MCI. The ERD/ERS results, presented by Missonnier et al. (2006a,b), indicate that a decrease in the early phasic theta power during working memory activation may predict cognitive decline in MCI. This phenomenon is not related to working memory load, but may reflect the presence of early deficits in directed, attention-related neural circuits in patients with MCI. Grunwald et al. (2002) reported decreased theta reactivity during haptic tasks over parieto-occipital regions in MCI, while Van der Hiele et al. (2007) suggested a loss of attentional resources during memory that not only memory but also impaired attention is encountered at the earliest stages of the disease (Perry and Hodges, 1999).

Babiloni et al. (2005) evaluated MEG upon application of visual delayed choice reaction time task in AD, vascular dementia, young and elderly healthy control subjects. Their analysis of event-related alpha desynchronization showed that the alpha ERD peak was stronger in amplitude in the demented patients than in the normal subjects. Cummins et al. (2008) evaluated event-related theta oscillations in MCI patients and elderly controls during performance of a modified Sternberg word recognition task. Their results demonstrated that MCI subjects exhibited lower recognition interval power than controls at left fronto-central electrodes.

Caravaglio et al. (2010) analyzed single-trial theta ERO responses in two time windows (0–250 ms; 250–500 ms) and compared the results to prestimulus theta power during both target tone and standard tone processing in AD patients and in elderly controls. They indicated that AD patients had an increased prestimulus theta response, but did not show a significant poststimulus theta power increase upon both target and nontarget stimulus processing. On the other hand, the healthy aged controls showed enhanced early and late theta responses in comparison to the prestimulus baseline only during auditory oddball paradigm.

Zervakis et al. (2011) analyzed event-related inter-trial coherence in mild probable AD patients and elderly controls upon stimulation of an auditory oddball paradigm. The authors reported that the theta band in AD patients is reflected in slightly more energy than in controls and the absence of nonphase-locked late alpha activity. They commented that the increase of theta responses in AD patients could be due to cholinesterase inhibitors, which all their AD subjects were taking.

According to the few published event-related oscillation studies (Yener et al., 2007, 2008, 2012; Caravaglio et al., 2008, 2010), frontal delta ERO responses are decreased in AD either in visual or auditory modality. In these studies, it was clearly demonstrated that the most affected frequency bands upon the application of the odd-ball paradigms were in theta and delta bands (Yener et al., 2007, 2008; Caravaglio et al., 2008, 2010). Theta oscillatory responses displayed lower values of phase-locking in frontal area in AD (Fig. 3; Yener et al., 2007). Delta oscillatory
response amplitudes, both upon application of visual (Fig. 4; Yener et al., 2008) and auditory odd-ball paradigms (Caravaglios et al., 2008; Yener et al., 2012) were decreased in fronto-central regions (Fig. 5). A gradual decrease of auditory delta oscillatory response amplitudes was seen among healthy control (HC), MCI, and AD groups (Yener et al., 2011, unpublished data), indicating a continuum between MCI and AD (Fig. 6). Caravaglios et al. (2008) found that neither pre-stimulus nor poststimulus delta ERO activity differed from controls in an AD group of 21 subjects. However, they showed that the reactivity of delta upon stimulus processing reduces over frontal regions. Yener et al. (2008) similarly found reduced amplitude in auditory delta ERO activity over central regions.

This reduction of frontal activity can be explained by Fuster’s (1990) findings, showing anticipatory activation in frontal neurons in time delay tasks in monkeys. Although earlier anatomical studies indicate less prominent pathologic involvement of frontal lobes (Braak et al., 1993), the latest findings on in vivo amyloid imaging in MCI subjects who convert to AD imply that amyloid deposits accumulate in lateral frontal lobes (Koivunen et al., 2011). Many different methods have shown that strong connections of frontal lobe and limbic and heteromodal cortical areas are also affected in early AD, resulting in decreased frontal lobe function (Leuchter et al., 1992; Grady et al., 2001; Delatour et al., 2004).

Phase-locking is a manifestation of synchronization between individual neurons of neural populations upon application of a sensory or cognitive stimulation. The sensory or cognitive inputs can originate from external physical signals or can also be triggered from internal sources. Several publications report phase-locking of theta oscillatory responses as a result of cognitive load in P300 target paradigm (Başar-Eroğlu et al., 1992; Demiralp et al., 1994; Klimesch et al., 2004). Healthy subjects show strong theta phase-locking in the frontal area in visual ERO responses (Fig. 3). The principle of superposition describes

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Fig. 3. Decreased visual ER theta phase-locking in AD. (Modified from Yener et al., 2007.)
integration over the temporal axis, consisting of a relationship between the amplitude and phases of oscillations in various frequency bands. In a pilot study (Yener et al., 2007) describing the phase-locking of event-related oscillations, unmedicated patients with AD showed weaker phase-locking than both healthy controls and AD subjects treated with cholinergic drugs. In the medicated AD patients and the controls, phase-locking following target stimulation was two times higher in comparison to the responses of the unmedicated patients (Fig. 3). The findings implied that the theta oscillatory responses at the frontal region are highly unstable in unmedicated mild AD patients, and that cholinergic agents may modulate event-related theta oscillatory activities.

It seems as though in slower frequency ranges (delta, theta), peak amplitudes following cognitive stimulus are decreased over frontal-central regions in AD, regardless of sensory modality (auditory or visual) (Figs. 4 and 5). Also, there is a continuum between the AD and MCI subjects’ event-related responses, observed as decreased delta amplitudes and delay in the latency of delta peak (Fig. 6; Yener et al., 2011).

16.3.4.3. Comparison of SEO and ERO responses
Amplitude analysis of digitally filtered SEO or ERO responses provides the opportunity to explore sensory or cognitive neurodynamics. Yener et al. (2009) compared SEOs and EROs of patients with AD using a visual oddball paradigm. Significant decreases in delta event-related oscillatory activity over central regions were seen in AD, whereas increased delta visual SEO responses were recorded at parieto-occipital regions where primary and secondary sensory areas were located (Fig. 7). For further information on methodological issues, the reader is referred to reviews by Başar et al. (2010) and by Güntekin and Başar (2010). Similar to these findings, by means of auditory oscillatory responses, Caravaglios et al. (2008) found significant enhancement in delta responses in healthy controls when compared to Alzheimer’s subjects (especially at

Fig. 4. Decreased visual ER delta oscillatory responses in AD over the central area. (Modified from Yener et al., 2008.)
Fig. 5. Auditory delta ERO responses are decreased in frontal regions in AD. (Modified from Yener et al., 2012.)
frontal locations). The lack of frontal delta responses, irrespective of stimulus modality, implies a decision-making impairment and decreased frontal functioning in mild AD.

Table 2 shows the latest studies of brain oscillations in AD.

16.3.5. Coherence

Coherence is a measure of synchrony between separate structures and it was first used five decades ago by Adey et al. (1960), as a pioneering work on theta rhythms of the cat limbic system during conditioning. Coherence (Gardner, 1992) or phase-locking statistics (Lachaux et al., 2002) are some of the common techniques used to evaluate relationships between neural populations. Coherence values range between 0 and 1, with higher values indicating better connectivity between two structures.

Adey et al. (1960) used spectral analysis and coherence functions to investigate how the rhythmic potentials of the cat brain were related to behavior. The use of the coherence function in comparing EEG activity in various nuclei of the cat brain was one of the essential steps in refuting the view that the EEG was an epiphenomenon. Accordingly, the induced theta rhythm and the task-relevant increase of coherence in the limbic...
system is a milestone in EEG research. When carrying out a behavioral task, the cat hippocampal activity exhibits a transition from irregular activity to coherent, induced rhythms. Sauseng et al. (2005) calculated the coherence function during a visuospatial working memory task in a group of healthy subjects. Their findings indicated that the involvement of prefrontal areas in executive functions are reflected in a decrease of anterior upper alpha short-range connectivity and a parallel increase of fronto-parietal long distance coherence, mirroring the activation of a fronto-parietal network.

Many studies reported the successful use of EEG coherence to measure functional connectivity (Lopes da Silva et al., 1980; Rappelsberger et al., 1982). According to these studies, EEG coherence may be regarded as an indispensable large-scale measure of functional relationships between pairs of cortical regions (Nunez, 1997). It is also important to mention the studies of T.H. Bullock’s research group (Bullock et al., 1995), which clearly showed that the connectivity (coherence) between neural groups is a main factor for the evolution of cognitive processes (Başar et al., 2010). According to Bullock and Başar (1988) and Bullock et al. (1995), no significant coherences were found in the neural networks of invertebrates, in contrast to the higher coherences between distant structures that were recorded in mammalian and human brains. The highest coherences were found in the subdural structures of the human brain (Bullock,

Fig. 7. Comparison of visual evoked and ER oscillatory activity in AD. (Modified from Yener et al., 2009.)
## TABLE 2
THE EVOKEO', AND EVENT-RELATED OSCILLATION STUDIES IN AD/MCI IN RECENT YEARS

<table>
<thead>
<tr>
<th>Studies on MCI/AD subjects</th>
<th>Modality and paradigms</th>
<th>Subjects Methods</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td><strong>Evoked oscillatory activity</strong></td>
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<tr>
<td>Kikuchi et al. (2002)</td>
<td>Visual photic stimulation</td>
<td>AD</td>
<td>Evoked coherence</td>
</tr>
<tr>
<td>Hogan et al. (2003)</td>
<td>Visual photic</td>
<td>AD</td>
<td>Evoked coherence</td>
</tr>
<tr>
<td>Zheng-yan (2005)</td>
<td>Visual photic</td>
<td>AD</td>
<td>Evoked coherence</td>
</tr>
<tr>
<td>Osipova et al. (2006)</td>
<td>Auditory steady state</td>
<td>AD</td>
<td>40 Hz SSR</td>
</tr>
<tr>
<td>Haupt et al. (2008)</td>
<td>Visual checkerboard stimulation</td>
<td>AD/MCI</td>
<td>Evoked oscillatory response</td>
</tr>
<tr>
<td>Başar et al. (2010)</td>
<td>Visual evoked</td>
<td>AD</td>
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</tr>
<tr>
<td>Yener et al. (2009)</td>
<td>Visual evoked</td>
<td>AD</td>
<td>Evoked oscillatory response</td>
</tr>
<tr>
<td>Van Deursen et al. (2011)</td>
<td>Auditory steady state</td>
<td>AD/MCI</td>
<td>40 Hz SSR</td>
</tr>
<tr>
<td><strong>ER oscillatory activity</strong></td>
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<tr>
<td>Babiloni et al. (2005)</td>
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<td>Auditory Sternberg word test</td>
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</tr>
<tr>
<td>Missonnier et al. (2007)</td>
<td>N-back test</td>
<td>MCI/AD</td>
<td>ERD/ERS</td>
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<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. (2007)</td>
<td>Three-level working memory test</td>
<td>MCI</td>
<td>Inter- and intra-hemispheric coherence</td>
<td>Interhemispheric coherence is increased more than intra-hemispheric coherence in MCI</td>
</tr>
<tr>
<td>Yener et al. (2007)</td>
<td>Visual oddball</td>
<td>AD</td>
<td>Event-related phase-locking</td>
<td>Decreased theta phase-locking at the left frontal in untreated AD in comparison to controls and cholinergically treated AD</td>
</tr>
<tr>
<td>Polikar et al. (2007)</td>
<td>Auditory oddball</td>
<td>AD</td>
<td>ERO response</td>
<td>1–2 and 2–4 Hz at Pz, Cz, 4–8 Hz at Fz provide the most discriminatory information for automated classification</td>
</tr>
<tr>
<td>Cummins et al. (2008)</td>
<td>Auditory Sternberg word test</td>
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</tr>
<tr>
<td>Yener et al. (2008)</td>
<td>Visual oddball</td>
<td>AD</td>
<td>ERO response</td>
<td>Decreased delta oscillatory peak-to-peak amplitudes at central electrodes</td>
</tr>
<tr>
<td>Güntekin et al. (2008)</td>
<td>Visual oddball</td>
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<td>Event-related coherence</td>
<td>Decreased alpha, theta, delta event-related coherence between frontal and all connections</td>
</tr>
<tr>
<td>Van Deursen et al. (2008)</td>
<td>Music and story listening, visual task</td>
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<td>A significant increase of gamma band power in AD cases compared to healthy controls and MCI cases</td>
</tr>
<tr>
<td>Caravaglios et al. (2008)</td>
<td>Auditory oddball</td>
<td>AD</td>
<td>ERO response</td>
<td>Decreased enhancement of the delta response in single sweep maximal peak-to-peak amplitude especially at the frontal location in AD</td>
</tr>
<tr>
<td>Deiber et al. (2009)</td>
<td>N-back paradigm</td>
<td>MCI</td>
<td>ERS</td>
<td>Decreased induced theta activity in progressive MCI than stable MCI or controls</td>
</tr>
<tr>
<td>Missonnier et al. (2010)</td>
<td>Visual N-back task</td>
<td>MCI</td>
<td>ERO response</td>
<td>Progressive MCI cases displayed higher gamma values and reduced theta than stable MCI cases</td>
</tr>
<tr>
<td>Caravaglios et al. (2010)</td>
<td>Auditory oddball</td>
<td>AD</td>
<td>ERO response</td>
<td>Increased prestimulus theta power, and lack of poststimulus theta power in AD. Healthy controls had a frontal dominance of theta power</td>
</tr>
<tr>
<td>Polikar et al. (2010)</td>
<td>Auditory oddball</td>
<td>AD</td>
<td>ERO response</td>
<td>The ERO + MRI parameters together show as high accuracy rates (80%) as PET + MRI parameters for classification of AD</td>
</tr>
</tbody>
</table>
Since coherence is, in essence, a correlation coefficient per frequency band, it is used to describe the coupling or relationship between signals for a certain frequency band. According to Bullock et al. (2003), increased coherence between two structures, namely A and B, can be caused by the following processes: (1) structures A and B are driven by the same generator; (2) structures A and B can mutually drive each other; and (3) one of the structures, A or B, drives the other (Fig. 8). There are several synchrony measures studied in AD diagnosis, including the correlation coefficient, mean square, phase coherence, Granger causality, phase synchrony indices, information theoretic divergence measures, state-space-based measures, and stochastic event synchrony measures. Among these, Granger causality and stochastic event synchrony measures were used to distinguish MCI from healthy controls, achieving an accuracy of 83% (Dauwels et al., 2010b).

### 16.3.5.1. SE coherences

EEG coherence globally describes the coupling of, or relationship between, signals in a given frequency band. The term “sensory evoked (SE) coherence” reflects the property of sensory networks activated by a simple sensory stimulation without a cognitive load, whereas “event-related (ER) coherence” manifests coherent activity of sensory and cognitive networks triggered by a cognitive task, i.e., oddball paradigm (Fig. 9). According to Başar et al. (2010) the results of SE coherence show that the coherence values in all frequency ranges do not exceed 0.35 (Fig. 10), whereas ER coherence values elicited upon a cognitive paradigm reach 0.7. Thus, the comparison of ER and SE coherences demonstrates that sensory signal elicits only negligible coherence values in comparison to the results of a cognitive task.
Rossini et al. (2006) measured the spontaneous EEG coherences in healthy controls and two groups of MCI (progressive and stable) and found that progression to conversion is faster in patients with high coherence in delta and gamma frequency bands. Later Babiloni et al. (2010) demonstrated that total coherence of alpha rhythms was highest in the healthy elderly, intermediate in the MCI subjects with no cholinergic white matter lesion, and lowest in the MCI with cholinergic lesion. Furthermore, damage to the cholinergic system is associated with alterations of the functional global coupling of resting alpha rhythms.

The topography of changed connectivity in AD upon visual simple sensory stimulation is not straightforward. Hogan et al. (2003) examined memory-related EEG power and coherence over temporal and central recording sites in patients with early AD and normal controls. While the behavioral performance of very mild AD patients did not differ significantly from that of normal controls, when compared with normal controls, the AD patients had reduced upper alpha coherence between the central and right temporal cortex. Zheng-yan (2005) stated that during photic stimulation, inter- and intrahemispheric EEG coherences of the AD patients showed lower values in the alpha (9.5–10.5 Hz) band than those of the control group.

Taken together, these results indicate that the sensory network is affected in AD; however, the severity of dysfunction does not seem to be as high as that in the cognitive network (Figs. 10 and 11).

16.3.5.2. ER coherences
ER coherences manifest coherent activity of sensory and cognitive networks triggered by attending to a cognitive task. Accordingly, the cognitive response coherences comprehend activation of a greater number of neural networks that are most possibly not activated, or less activated than the spontaneous EEG or SE coherences (Fig. 9). Therefore, ER coherence merits special attention. Particularly in AD patients with strong cognitive impairment, it is relevant to analyze whether medical treatment (drug application) selectively acts upon sensory and cognitive networks manifested in topologically different areas and in different frequency windows. Such an observation may provide a deeper understanding of distributed functional networks and, in turn, the possibility of determining biomarkers for medical treatment. According to the statements above, there are new steps and newly emerging questions. Güntekin et al. (2008) investigated ER coherence of patients with mild AD using a visual oddball paradigm. The AD group was divided into unmedicated and the medicated (cholinergic) subgroups. The authors found that the control group showed higher ER coherence in the “delta,” “theta,” and “alpha” bands compared to the unmedicated AD group (Fig. 12; Başar et al., 2010). Alpha ER coherence values were higher in the medicated AD subjects than

![Fig. 9. Neural assemblies involved in sensory and cognitive networks. Cognitive networks (here shown by magenta lines) probably contain sensory neural elements, but also involve additional neural assemblies as shown by magenta circles. Sensory network elements are illustrated by blue squares and connections by blue lines. It is expected that sensory signals trigger activation of sensory areas, whereas cognitive stimulation would evoke both neural groups reacting to sensory and cognitive inputs.](image-url)
in the unmedicated group. This finding implies better connectivity with the use of cholinergic drugs in AD.

16.3.5.3. Comparison of SE and ER coherences
Coherence values range between 0 (lowest) and 1 (highest). Upon application of an oddball paradigm, the ER coherences between left fronto-parietal (F3 and P3) locations could show significant coherences of up to 0.7 in the theta, delta, and alpha frequencies in healthy subjects (Fig. 10). Unmedicated AD subjects showed a reduction of 30–40% in theta, delta, and alpha frequency ranges compared with both the controls and the medicated AD subjects. In the medicated group, the coherence of alpha frequency was restored, whereas in theta and delta ranges the cholinergic medication did not cause any change in coherence. It should be emphasized that values in the range of 0.6–0.7

Fig. 10. Coherences of brain oscillations upon a cognitive task (i.e., target stimulus in classical visual oddball paradigm) reach higher values than those elicited upon simple sensory visual stimuli (i.e., basic light stimulation). Coherence, which reflects functional connectivity between fronto-parietal regions, is higher in controls than in (AD) subjects. Coherence values in alpha ranges are greater in the cholinergically treated subgroup than those with no treatment. (Modified from Yener et al., 2010.)

Fig. 11. Visual SEO responses in AD are not that different from that of controls with the exception of a mild decrease in delta band between the left frontal and occipital regions. (Modified from Başar et al., 2010.)
indicate significantly high coherence values, because of the long distance between frontal and parietal location. According to Güntekin et al. (2008), the results emphasized that left fronto-parietal connections are highly affected by AD pathology, occurring primarily within the fronto-parietal limbic regions during the early stages of the disease. Fig. 10 compares SE coherences and event-related coherence following target stimulation at F3-P3 electrode pairs during an oddball paradigm.

Zheng-yan (2005) reported that, during photic stimulation, AD patients showed reduced inter and intrahemispheric coherences in the alpha (9.5–10.5 Hz) band than those of the control group. During a 5-Hz photic stimulation, the AD patients had significantly lower intrahemispheric coherence in theta, alpha, and beta bands. Hogan et al. (2003) examined memory-related EEG power and coherence over temporal and central recording sites in patients with early AD and found that dementia subjects had reduced upper alpha coherence between the central and right temporal cortex than observed in the healthy control group. Zheng et al. (2007) investigated inter and intrahemispheric coherence during a three-level working memory task undertaken by patients with MCI. The coherence in MCI patients was significantly higher than in the controls. Their findings indicate that the alpha frequency band for coherence studies may be the characteristic band in distinguishing MCI patients from normal controls during working memory tasks. MCI patients exhibit larger interhemispheric connectivity than intrahemispheric connectivity when memory demand increases.

Coherences between prefrontal–parietal and prefrontal–occipital regions may have a role in determining the resulting activity in parietal or occipital regions. Our groups’ findings on coherences (Güntekin et al., 2008; Başar et al., 2010) are consistent with functional imaging studies in AD, showing relatively large attenuation of activations in parieto-occipital (Bradley et al., 2002; Prvulovic et al., 2002; Bentley et al., 2008) than in temporo-occipital areas. The observed hyperexcitability of primary visual areas following simple visual stimulation in AD
(Yener et al., 2009) could be partially related to several factors: (1) the decreased SE coherence (connectivity) between frontal and posterior parts of the brain; (2) the decreased frontal lobe modulation (Yener et al., 2007, 2008; Caravaglios et al., 2008, 2010); and (3) the relatively preserved sensory and motor cortical areas (Braak et al., 1993). The motor cortex hyperexcitability in AD was previously shown by Ferreri et al. (2003).

Furthermore, selectively distributed and selective coherent oscillatory activities in neural populations describe integration over the spatial axis (Başar, 1980). Consequently, integrative activity is a function of the coherences between spatial locations of the brain. These coherences vary according to the type of sensory and/or cognitive event and possibly the state of consciousness of the species (Başar, 1999, 2004). The work of Bressler and Kelso (2001) emphasized that within the coordinated large-scale cortical network, the participating sites are much more interrelated to one another than to non-network sites. These coordinated areas undergo re-entrant processing, and later re-entrant interactions will constrain the local spatial activity patterns in these areas. In this manner, re-entrant transmissions define local expression of information. As areas interact reciprocally, some areas reach a consensus through the process of large-scale relative coordination, in which those areas temporarily manifest consistent local spatial activity patterns. This mechanism also provides dynamic creation of local context in a highly adaptive manner in visual functions. Varela et al. (2001) state that the emergence of a unified cognitive moment depends on the coordination of scattered parts of functionally specialized brain regions. The mechanisms of large-scale integration enable the emergence of coherent behavior and cognition. These authors argue that the most plausible candidate is the formation of dynamic links mediated by synchrony over multiple frequency bands. Von Stein and Sarter (2000) propose that long-range fronto-parietal interactions during working memory retention and mental imagery evolve, instead, in the theta and alpha (4–8 Hz, 8–12 Hz) frequency ranges. This large-scale integration is performed by synchronization among neurons and neuronal assemblies evolving in different frequency ranges.

16.4. Neurotransmitters

The dysfunction of cognitive network in AD may be a result of balance disorder between neural excitation and inhibition through neurotransmitters, and disorder of long-term potentiation that strengthens or weakens the synaptic connections (Lisman and Spruston, 2005).

16.4.1. Main neurotransmitter systems and their effects on cognitive network

Acetylcholine (ACh)-containing projections from the nucleus basalis Meynert degenerates first in AD (Mesulam et al., 2004). This depletion seems to have a role in dysfunction in visuospatial system and memory-related tasks in AD. ACh promotes visual feature detection or signal-to-noise ratios in sensory processing (Hasselmo and Giacomo, 2006) and cholinergic medication can improve a normal pattern of task-dependent parietal activation in AD. Working memory tasks (Saykin et al., 2004), visual search (Hao et al., 2005), or visual attention (Balducci et al., 2003) studies indicate enhanced prefrontal cortex activity after cholinergic medication, similar to the electrophysiological findings shown by our group (Yener et al., 2007; Güntekin et al., 2008). An fMRI study in mild AD/MCI also showed a similar pattern in left prefrontal regions during attentional demands (Dannhauser et al., 2005). The diffuse innervation of cortical cholinergic neurons (Sarter et al., 2001) can lead to cholinergic modulation in both higher-level (e.g., fronto-parietal) and lower-level (e.g., visual) areas. It is possible that visual ERO deficits in AD may be related to reduction in cholinergic modulation of visual cortex and attention-related fronto-parietal cortices (Perry and Hodges, 1999).

Understanding how the cholinergic system affects visual sensory or cognitive function is important for AD. When two types of tasks (i.e., deep minus shallow visual stimulation) were given to AD patients
and controls, fMRI showed that the right parietal (Hao et al., 2005), left prefrontal, and superomedial prefrontal cortices were less activated by this task effect in AD patients than in controls (Bentley et al., 2008). The extent of involvement of visual and higher order association cortex increased with greater complexity in AD. Visual tests activate both primary and secondary visual areas in dorsal stream ( Förster et al., 2010). Visual dorsal stream, which involves the parietal lobe, is activated before the ventral stream, which includes the temporal lobe. The parietal lobe is activated within 30 ms after occipital activation, occurring at about 56 ms. Visual sensory areas generally continue to be active for 100–400 ms prior to motor output. The feedback processes between sensory, parietal, and prefrontal cortices take about 200 ms for an interactive process. This initial volley of sensory afference through the visual system, and involving top-down influences from parietal and frontal regions, occurs much earlier than the early ERP components ( Foxe and Simpson, 2002). Using visuospatial paradigms, these regions are particularly sensitive to cholinergic modulation (Sarter et al., 2005). Acetylcholine seems to have a role in promoting visual feature detection or signal-to-noise ratios in sensory processing (Hasselmo and Giocomo, 2006) and cholinergic medication can improve a normal pattern of task-dependent parietal activation in AD.

16.4.2. Changes in AD subjects on cholinergic medication

Cortical ACh is hypothesized to modulate either the general efficacy of the cortical processing of sensory or associational information, or, more specifically, to mediate the subjects’ abilities to select stimuli and associations for further processing (Sarter et al., 2005). The basal forebrain is the main source of ACh in the neocortex and Alzheimer patients show depletion of cortical ACh due to degeneration of the basal forebrain early in the course of the illness (Mesulam et al., 2004). Therefore, for almost the past 20 years, cholinergic treatment was the main treatment option in AD. In addition, increased cholinergic input can restore hemodynamics in clinical responders (Claassen and Jansen, 2006). An early study on resting EEG showed that alpha power decreased following experimental damage to this cholinergic pathway (Holschneider et al., 1998). In addition to the basal forebrain, glutamatergic and cholinergic mechanisms within the prefrontal cortex may also regulate ACh release in other parts of the cortex such as the posterior parietal cortex (Nelson et al., 2005). The ability of prefrontal cortex to regulate transmission in more posterior cortical regions may represent a “top-down” mechanism to control attention (Sarter et al., 2005). For example, thalamocortical fibers are suppressed much less than intracortical connections by acetylcholine, thus possibly enabling the afferent input to have a relative effect in the cortex (Kimura et al., 1999). Therefore, the detrimental performance effects of an ongoing distracter are most likely diminished by increasing the cholinergic processing of sensory inputs (Sarter et al., 2005). These agents can improve the latencies of the visual P300 in AD patients (Reeves et al., 1999). Earlier functional imaging studies showed that, after administration of AChEI, clinical responders to treatment selectively displayed improvements over left cingulate and prefrontal–parietal areas (Potkin et al., 2001; Nobili et al., 2002; Vennerica et al., 2002; Mega et al., 2005).

16.5. Summary

The results of the present review permit tentative concluding remarks related to neurophysiological markers for AD patients. In defining one type of neurophysiological marker, we prefer to categorize the presented results according to their functions: (a) spontaneous EEG or resting EEG; (b) SEO responses and coherences following a simple sensory stimulus without a cognitive load; and (c) ERO responses and coherences following a cognitive stimulus (i.e., oddball paradigm). Our tentative proposal indicates that the collection of information, and especially their comparison, could provide a
solid construct as “an ensemble of neurophysiologic biomarkers.” Furthermore, we propose that this type of strategy will be useful for analysis of neuropsychiatric disorders in general (see Yener and Başar, this volume).

16.5.1. Spontaneous EEG activity

An extended review of spontaneous EEG activity of AD/MCI patients is described by Vecchio et al. in this issue. The spontaneous EEG activity of AD shows characteristically increased delta and theta power in temporo-occipital regions and decreased power in beta and alpha power in parieto-occipital regions. Also, fronto-parietal coherences were abnormal in amnesic MCI, reflecting a functional disconnection among cortical regions.

16.5.2. SE oscillations

Some brain areas (sensorial and motor cortices) seem to be hyperexcitable in AD, as shown by increased theta responses over primary and secondary sensory areas (Yener et al., 2009), and increased gamma responses (Haupt et al., 2008; Van Deursen et al., 2011). The hyperexcitability of the sensory areas is indicated by the findings of Ferreri et al. (2003) and Rossini et al. (2006), indicating hyperexcitability of motor cortex in AD. These findings are in accordance with relative preservation of primary sensory and motor cortical areas in this disorder. It is highly important to note that pure sensory stimulation in AD does not display a remarkable change in frontal brain regions from that of healthy controls (Table 1 and Fig. 7).

16.5.3. ER oscillations

Contrary to results on SEOs, the cognitive paradigm (EROs) elicits: (a) attenuated delta responses over frontal and central modulating regions (Figs. 5 and 6); (b) decreased frontal phase-locking (i.e., synchronization among single sweeps) in the theta frequency range (Fig. 4); and (c) improved theta phase-locking with cholinesterase inhibitor medication (Fig. 4 and Table 1).

16.5.4. Coherences

SE coherence elicited upon simple sensory stimulation displays decreased values between only frontal lobe and primary sensory (i.e., in visual tasks, occipital) regions in the delta frequency range (Fig. 11). However, event-related coherence recorded upon a cognitive task shows decreased values between frontal and all other brain connections in the many frequency ranges, including alpha, theta, and delta (Fig. 12). It is important to note that, in higher frequency ranges (beta, gamma), no significant changes are evident in coherences. This finding implies that selective connectivity is disturbed in AD depending on the cognitive load of stimuli. Furthermore, regardless of group effect, there was great difference in coherence values between those elicited after SE and ER stimulations. The event-related coherence values (approximately 0.70) were up to double those of SE coherence (approximately 0.35) (Fig. 10). This finding implies that, upon application of a cognitive task, greater brain connectivity is reached, as expected. In addition, cholinergic agents promote improvements in alpha event-related coherences in AD subjects (Table 1, Figs. 10 and 12).

16.6. Conclusion

The most important conclusion of the present review is the following: according to Luria (1966), there are no anatomical centers for the psychological functions of the mind. Mental functions, too, are the products of complex systems, the component parts of which may be distributed throughout the structures of the brain. The task of neuroscience is therefore not to localize the “centers” but, rather, to identify the components of the various complex
systems that interact to generate the mental functions. Luria called this task “dynamic localization.” Mental functions, in short, are not localized in any of the component structures, but rather distributed between them. Like the mental apparatus as a whole, they are virtual entities (Solms and Turnbull, 2002). According to the present review, the understanding of whole brain function also requires the analysis of functional coherences, i.e., the increased connectivity between structures upon cognitive load, together with enhanced temporal oscillatory responses. Furthermore, in addition to Luria’s view, it seems that Brodmann’s areas should be extended to a more dynamic presentation, in which sensory and cognitive areas should be described as superposition of multiple primary and secondary functions.

Only in this way it may be possible to open new avenues for description of whole cortex organization. As a consequence, we propose that all information gathered from sensory or cognitive paradigms must be jointly analyzed in terms of oscillatory responses and related coherences in order to validate an electrophysiological biomarker. We tentatively assume that prefrontal areas have a modulating effect on other parts of the brain, depending on stimulation modality (i.e., sensory or cognitive). However, the modulation of the prefrontal lobe may be different on the projecting areas, depending on the cognitive load of the stimulus and on interconnected brain areas, such as primary sensory, primary motor, or heteromodal cortical areas. Among the electrophysiological parameters, the ER (or cognitive) coherences comprehend activation of a greater number of neural networks and merit special attention among the assembly of electrophysiological parameters. Therefore, ER coherence variables can be suggested as a candidate electrophysiological biomarker for diagnosis and monitoring of treatment effects in AD in the first instance. Other methods, such as phase-locking, may also provide insights into cognitive networks and their modulation by neurotransmitter changes. Oscillatory response peak-to-peak amplitudes, especially those in delta frequencies at frontal locations, seem to be a candidate for a static (i.e., for using in diagnosis), rather than a dynamic (i.e., for understanding change over time or in response to medication) biomarker.

The results presented in this review provide evidence for the existence of separate sensory and cognitive networks that are activated either on sensory or on cognitive stimulation and show the group differences. These observations may serve to increase the physiological understanding of distributed functional networks and, in turn, the possibility of determining biomarkers for either diagnosis or monitoring of medical treatment in AD/MCI. However, it is also important to state that a greater number of subjects are needed to study either the effects of pharmacological applications or its diagnostic role on an individual basis. The standardization and harmonization of user-friendly acquisition and analysis protocols in larger cohort populations must be the main focus among researchers working on this field in order to incorporate electrophysiology as a part of the clinical criteria of AD.

**Abbreviations**

Aβ42 = amyloid β42 peptide
ACh = acetylcholine
AD = Alzheimer’s disease
ADHD = attention deficit hyperactivity disorder
ADNI = Alzheimer’s disease neuroimaging initiative
ASSR = auditory steady-state responses
BD = bipolar disorder
CSF = cerebrospinal fluid
EEG = electroencephalography
ER = event-related
ERO = event-related oscillation
fMRI = functional magnetic resonance imaging
FDG-PET = fluorodeoxyglucose positron emission tomography
MCI = mild cognitive impairment
MRI = magnetic resonance imaging
PIB-PET = Pittsburgh compound B positron emission tomography
PLF = phase-locking factor
P-tau = phospho-tau protein
SE = sensory evoked
SEO = sensory-evoked oscillation
TMS = transcranial magnetic stimulation
T-tau = total tau protein

References


