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EEG and ERP biomarkers of Alzheimer's disease: a critical review

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1. ABSTRACT

Here we critically review studies that used electroencephalography (EEG) or event-related potential (ERP) indices as a biomarker of Alzheimer's disease. In the first part we overview studies that relied on visual inspection of EEG traces and spectral characteristics of EEG. Second, we survey analysis methods motivated by dynamical systems theory (DST) as well as more recent network connectivity approaches. In the third part we review studies of sleep. Next, we compare the utility of early and late ERP components in dementia research. In the section on mismatch negativity (MMN) studies we summarize their results and limitations and outline the emerging field of computational neurology. In the following we

overview the use of EEG in the differential diagnosis of the most common neurocognitive disorders. Finally, we provide a summary of the state of the field and conclude that several promising EEG/ERP indices of synaptic neurotransmission are worth considering as potential biomarkers. Furthermore, we highlight some practical issues and discuss future challenges as well.

2. INTRODUCTION

Alzheimer's disease is the most common cause of cognitive decline in the elderly creating significant medical and economic burden. Approximately 47 millions of people live with

neurocognitive disorders worldwide, and this number is expected to triple by 2050 (1). Despite the huge efforts to find accurate treatment for AD, we are still not able to influence the progression of the disease. One of the reasons for this failure is that the pathological changes start decades before the initial clinical symptoms (2). The neuropathological hallmarks of AD are the presence of extracellular amyloid plaques and the intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Growing body of evidence (3) suggests that the misfolded proteins might compromise the synaptic functions leading to severe network disintegration. Recent studies have illustrated that abnormal tau and amyloid could modify the pre- and postsynaptic neuronal mechanisms, elevate the neuronal calcium influx leading to increased excitability, neuronal loss and altered rhythmic patterns (4–6). Synaptic plasticity is essential in all complex cognitive functions such as learning, abstract thinking and memory (7). Evidence from recent neurophysiological and pathological studies suggests that impaired synaptic plasticity is a dominant feature of AD (8). Intact synaptic plasticity seems to be essential to normal neuronal oscillatory synchronization, which is thought to be the basis of information transfer at cell population level in the human brain underlying cognitive functions by functionally integrating a distributed network neuronal populations (9). Only recently, we begin to see how compromised network functions may affect motor activity, perception, or more complex cognitive functions like memory formation or decision-making. The emerging view of neurological and psychiatric disorders as “oscillopathies” provides a new perspective that might help better understand clinical conditions (10). Based on these considerations, AD has recently been described as a network disconnection disease or as an oscillopathy (11).

Large-scale oscillatory neural population activity and event-related responses are often recorded using electroencephalography (EEG). EEG is a relatively cost-effective, non-invasive technique that provides *in vivo* data on electrical activity during neurotransmission with high temporal resolution. EEG has been successfully used in studying neurocognitive disorders, for example in schizophrenia (12), which has also been conceptualized as a dysconnection syndrome (13–14). Several characteristics of the EEG and event-related potentials (ERP) have been put forward as biomarkers in AD (15). Biomarkers are objective indicators of medical state that are sensitive and specific to a given pathology (16). Although a growing body of evidence indicates that EEG might be useful in the early recognition of neural signatures of dementia (17) as well as in the differential diagnosis of cognitive impairment (15, 18), this technique is rarely involved in the protocols of clinical assessment of cognitive decline.

Here we summarize the current knowledge on potential EEG and ERP biomarkers with respect to their importance in the diagnosis of AD, in early recognition of cognitive impairment, in differential diagnosis of neurocognitive disorders, and their relation to neuroimaging and neuropsychological findings.

3. EEG STUDIES IN AD

3.1. Visual inspection and spectral characteristics of EEG in AD

The conventional visual inspection of the EEG is still a widely used diagnostic method of neurological assessment (e.g., 19). The disappearance of posterior dominant alpha rhythm and the diffuse slowing in AD are easily detectable EEG signs for the experienced eyes. These changes have been reported in numerous previous studies even in patients with pathologically confirmed diagnosis (35 AD patients in the study of Brenner et al., (20)) and 72 patients in the study of Gordon et al., (21)). Strong correlation between visual EEG scores and dementia severity assessed by Mini Mental State Examination (MMSE) has been reported (22–23). In the study of de Waal et al. with 460 AD patients, subjects with early onset AD presented more severe diffuse slowing compared to the later onset counterparts, which is in line with the clinical presentation of AD (23). Based on these findings, the visual inspection of the EEG seems to be useful in the evaluation of AD.

Spectral analysis of EEG signals by Fourier or wavelet transformation has been widely used in the research of neurological and psychiatric disorders, including cerebrovascular disorders and epilepsy. Originally, the method was suggested by Roy John with the aim of the differential diagnosis of brain dysfunctions (24). Spectral methods estimate the power of selected EEG frequency bands, and the results are often evaluated with regard to their topographical distribution. Early spectral EEG studies revealed that a shift to lower frequency rhythms, i.e., a diffuse slowing of the EEG is a prominent feature of AD. Specifically, a reduction of power in the alpha (8–15Hz) and beta (16–31Hz) bands, as well as an increase in the theta (4–8Hz) and delta (0.5–4Hz) bands have been observed (25–26). Studies on higher frequency brain activity such as gamma oscillations yielded conflicting results (11). While Stam and his colleagues reported the loss of gamma band synchronization using magnetoencephalography (MEG) (27), other EEG (28–29) and MEG (30) studies found an increase in gamma power. Some studies indicate that in the diagnosis of AD the measurement of theta power could be as sensitive as the measurement of regional glucose metabolism by PET. In the studies of Szeliés on 24 AD patients, the differentiation of AD and age matched healthy elderly using relative theta

power was correct in 86% while it was correct in 87% when assessing temporo-parietal glucose metabolism (31–32).

It has also been shown that spectral changes show specific topographical distribution. Earlier studies with low sample size (12 and 8 AD patients) reported that the increase of lower frequency bands typically appeared over the left temporal area (33–34). The difference between mild AD and normal healthy controls seemed to be the most prominent in the temporal area, while comparing advanced AD patients with controls the difference was mainly related to the mid-frontal and anterior bifrontal areas (35). In a study involving higher number of patients ($n=48$) using low resolution brain electromagnetic tomography (LORETA), Babiloni and his colleagues demonstrated that patients with mild AD had a significant attenuation in the low alpha band in temporo-parietal and limbic sources compared to age-matched normal individuals (36). In the experiment of Kwak (37), the left anterior alpha power was lower in patients with a Clinical Dementia Rating Scale (CDR) value of 0.5, compared to cognitively normal elderly. In CDR the 0 value represents the normal population, the 0.5 is very mild dementia, 1 is mild dementia, and 2 is moderate dementia, while 3 means severe dementia. Posterior theta power was increased bilaterally and power in all alpha bands was reduced in CDR 1 patients; while all alpha and beta power was reduced and the theta spectral power was increased in the CDR 2 patients; and alpha and beta spectral power was reduced and delta and theta spectral power was increased in the CDR 3 group (37). These changes are in line with the well-known pathological progression of the misfolded protein aggregation (38) suggesting that spectral alterations might indicate the severity of the disease (39).

Numerous studies with great samples have reported that spectral EEG measures showed a relationship to scores on common neuropsychological tests assessing cognitive functions. Significant correlation was revealed between the results of MMSE, Global Deterioration Scale (GDS), Addenbrooke Cognitive Examination (ACE) and qEEG parameters such as occipital peak frequency, reduction of alpha and beta spectral powers and increase in theta and delta spectral powers (37). In 69 subjects with mild cognitive impairment (MCI) and AD the delta power negatively correlated with MMSE scores, while alpha power showed a positive correlation (40). The decrease in alpha power was also found to be correlated with scores in the Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) in a study with 130 patients (41). In the experiment of Claus et al. involving 82 patients, Cambridge Cognition Examination (CAMCOG) scores showed similar results (42). Only one early study reported a minimal or no correlation between the EEG and the

neuropsychological test results; however, this study examined dementia patients with different etiology including AD, frontotemporal dementia, multi-infarct dementia and alcoholic dementia patients. (43).

Correlations between EEG changes and neuroimaging findings have been reported in many studies as well. Global alpha and delta power showed a relationship to the volumetric changes of sub-cortical white matter in a study with 65 AD and 34 MCI patients (44), to the level of hippocampal atrophy in 35 AD and 88 MCI patients (45), to the grey matter density of the thalamus and basal ganglia in 88 MCI patients (46) and to the volume of cortical grey matter in 108 AD and 102 MCI patients (47). In an earlier study, qEEG (prominently the relative theta power) could predict dementia severity with similar power as PET markers (32). The combination of MRI, PET, P300 EEG analysis and spectral EEG power analysis increased the accuracy of dementia diagnosis by 10–20% compared to a single diagnostic method (48). These findings indicate that qEEG might be useful to assess the severity and progression of AD (49).

Pathologic changes in AD are generally assumed to start several years before initial symptoms of cognitive deterioration appear (50). There is an urgent need to identify the disease in the prodromal or in the early clinical phases such as MCI. To address this, Jelic et al. studied spectral EEG properties in 27 MCI and 15 AD patients and found that the MCI group did not differ from the healthy controls in the baseline EEG measures. However, MCI patients had significantly lower relative theta power at the left temporal, temporo-occipital, centro-parietal and right temporo-occipital derivation compared to the AD group (50). In other studies with larger samples (69 MCI, 73 AD, and 64 control subjects), an increase in the relative theta-power and a decrease in alpha indicated well the conversion of MCI to AD. In LORETA studies, patients with MCI exhibited a reduction in centro-temporal, posterior delta and left anterior theta fields (51). In another study the same group found that amnesic MCI patients represent an intermediate stage between normal cognition and mild AD based on parietal and occipital power in the low alpha frequency band (47). A study by Huang et al. with 38 AD, 31 MCI and 24 control participants reported an anterior shift of the maximum alpha and beta power in AD compared to MCI (52). Based on longitudinal studies with 39 patients, the increase of delta and theta power and the decline in the alpha and beta band power are the most important predictors of conversion from MCI to AD within 1- and 2-year follow-ups (53–54). EEG studies have also showed differences in genetic mutation carriers of AD without memory complaints compared to non-carriers. Studies revealed that there is no difference between the apoE carriers and normal individuals; however, the presence of an apoE4 allele was associated with the

manifestation of synchronous high-voltage delta and theta activity as well as sharp-waves. Furthermore, hyperventilation induced significantly higher decrease in the alpha power and increase in delta-theta relative powers by the carriers in the studies of Ponomareva and colleagues involving altogether 572 individuals (55–58). Another study with 118 patients illustrated that apoε4 carriers show more frequent focal or global irregular slow wave activities after a traumatic brain injury (59). Interestingly, a recent study with lower number of participants revealed that patients (n=21) with presenilin-1 mutation show a significant decrease of the fast frequency bands prominently in the temporal regions compared to non-carriers even in the asymptomatic phase (60). These studies suggest that markers based on spectral EEG measures could be useful in the early identification of AD.

EEG studies on AD patients revealed that decrease in alpha power and increase in delta are the most prominent features of Alzheimer's disease, showing a strong relationship to neuropsychological test results (40–42) and structural brain alterations (44–47). Spectral changes in the delta and alpha band also indicate the conversion of MCI to AD (51). Theta power increase has also been suggested as a predictor for conversion of MCI to AD (51, 53). Reduced beta power has been reported in AD suggesting that it might be useful in the monitoring of MCI-AD conversion as well (37, 52). The changes of gamma band in AD and MCI are still ambiguous (27–30). These alterations together underlie the typical visual EEG appearance of AD, the diffuse slowing (23).

Simple measures of power at different frequencies fail to capture one of the most important features of the EEG signal, namely the dynamic coupling between the different oscillating populations. However, cognitive functions are supported by dynamic interactions between spatially separated but temporally coordinated brain networks. After the introduction of the disconnection theory by Delbeuck and his coworkers to dementia research, methods focusing on the measurement of functional connectivity between distributed brain areas have been applied more frequently in the field (61). The theoretical assumptions underlying these measurements is that rhythmic EEG activity in resting state reflect phase and/or amplitude coupling of oscillations in different neuronal populations. Such measures provide information about functional integration and segregation between oscillating populations, captured by synchrony between the EEG signals recorded at various electrode pairs (62). Spectral coherence is thought to indicating functional coordination between two or more EEG generators (63). For example, higher coherence values have been observed between brain regions with higher interactions and stronger associations

during perceptual and motor processes (64). It has been postulated that cholinergic pathways play an organizing function and modulate coherence across distant brain areas (65). It is strongly supported by a study demonstrating that scopolamine with anticholinergic effect reduces the EEG coherence (66). Because of the structural damage of the generators and the involvement of cholinergic basal forebrain neurons in AD (67), coherence studies pointed out significant alterations. Major decrease in coherence in the alpha band has been demonstrated in several studies, particularly at the left temporal region (n=31 AD patients) (68), with significant correlation to neuropsychological results (n=34 AD patients) (69). Delta coherence studies revealed conflicting results (68), but a recent study by Babiloni and his colleagues showed that AD patients have higher delta and theta coherence than normal controls (45). Global theta coherence increase was demonstrated in the study of Adler et al., but the interhemispheric theta coherence was significantly reduced (68). It should be noted that elevated delta coherence was also observed in MCI patients but in a lower extent compared to AD patients (70).

In summary, spectral power and coherence in different frequency bands might offer promising clinical tools for diagnosing AD, assessing the severity of cognitive decline, and they might contribute to early disease recognition (Table 1).

3.2. Non-linear EEG studies in AD

The basic concept of non-linear time series analysis of EEG rests on the assumption that the brain is a non-linear dynamical system thus its behavior follows the principles of chaos theory (71). EEG captures the large-scale spatio-temporal dynamics of electromagnetic fields in the brain which are thought to be generated by non-linear coupling interactions between different neuronal populations. According to Stam the trajectory of a non-linear dynamical system is determined by its initial state and the history of its evolution. It can be argued that such a system possesses memory since its current state is dependent on previous states (62). The first studies on non-linear dynamical properties of EEG have been published in the 80's and focused on primate spontaneous EEG and human sleep EEG (72). In the following years, a revolution took place in the field of non-linear EEG analysis focusing on modeling non-linear neuronal dynamics and on the development of new methods with the aim to analyze noisy, non-stationary and high-dimensional EEG. Numerous methods have been developed including non-linear forecasting, non-linear cross prediction, and dimension density; many of the novel methods relied on embedding the EEG time series in a multidimensional state-space and observing

Table 1. Changes in spectral power and phase coherence of different EEG bands in AD, MCI and preclinical stages of AD

EEG band	Spectral power and phase coherence in AD	Spectral power and phase coherence in MCI	Spectral power and phase coherence in preclinical AD
Gamma	IC	IC	DNA
Beta	↓↓	↓↓↓	↓↓
Alpha	↓↓↓	↓↓↓	↓↓↓
Theta	↑↑	↑↑	↑
Delta	↑↑↑	↑↑	↑↑↑

The number of arrows indicates the number of studies reporting concordant results: ↑ = 1–5 studies ↑↑ = 5–10 studies ↑↑↑ >10 studies. DNA = data not available; IC = inconclusive results.

different properties of resulting trajectories. For an exhaustive review see Stam (62).

It is well known that the pathological changes in AD affect not only specific brain regions but neural pathways between the major areas as well (73). Non-linear methods are commonly used in the research of AD comparing it to other psychiatric conditions, because of the widely accepted disconnection syndrome theory (59).

Correlation dimension (D_2) is one of the most commonly used non-linear EEG parameter in AD research. D_2 is a measure of the assumed independent variables that are required to precisely define the complexity of cortical dynamics reflected in the EEG signal. An early study with 21 AD and 29 MCI patients has shown that AD patients have lower D_2 values almost on every EEG channel suggesting a globally reduced complexity of the electric brain activity in AD (74). Normal elderly have significantly increased D_2 values in eyes-open state compare to eyes-closed state, while the difference disappears in AD, suggesting the loss of brain reactivity to external stimuli in AD (75). Further studies pointed out decreased complexity even in eyes-closed state in 15 AD patients compared to normal controls (76). These studies aimed to characterize the EEG in a global frequency range; however, the separate frequency bands are thought to represent different brain dynamic systems (26). Numerous studies investigated the complexity of EEG in different frequency ranges or multiple time scales. They identified higher D_2 at higher frequency ranges in 20 AD (77) and 17 AD patients (78), while lower values have been demonstrated in the low frequencies. Yosimura and colleagues investigated mild AD patients with the so-called omega complexity method and found high complexity in a wide range of frequencies similarly to the findings of Czigler and colleagues involving 12 AD patients (78–79). Omega complexity estimates the number of the independent, uncorrelated brain sources. Thus, these studies suggest the functional disintegration of cortical networks, with lower coherence between sources and a higher number of independent generators. A

decrease in the parameter that reflects flexibility of information processing, the so-called first positive Lyupanov exponent (L_1) has been also reported in some studies (27), which may represent a difficulty to enter different states from the initial one during information processing in AD.

Some new methods, such as multiscale entropy (MSE) have been implemented in the recent years enabling to investigate the complexity of dynamic biological signals across a long-range of temporal scales. These studies in 11 AD patients (80) as well as 26 AD and 22 MCI patients (81) found that AD patients had less complexity at smaller temporal scales related to higher frequency bands and higher complexity at larger temporal scales regarding lower frequency bands (80–81). Higher complexity in large temporal scales was strongly associated to the extent of cognitive decline. Studies of global range complexity yielded diverging results. However, different frequency bands correspond to different brain functions (82). While higher-frequency bands are thought to support local neuronal communication in smaller neuron groups with short-range neural connectivity, slower oscillations likely arise from larger populations within wider-range networks (83). Although finding a physiological interpretation of complexity measures obtained with methods motivated by dynamical system theory is not straightforward, these results are in line with the notion that AD is characterized by a disruption of integration and segregation within distributed brain networks (61).

Complexity measurements have shown a strong correlation also with results of neuropsychological tests. Lower global dimensional complexity was associated with lower MMSE scores in 21 AD patients (74). The estimated severity of the disease also showed a strong relationship to non-linear measures in the study of Besthorn involving 50 AD patients (84). Region-specific changes were observed in the study of Ikawa et al., where a strong association was found between the reduced dynamical complexity (DC) in the mid-temporal, left frontal, central areas and cognitive status in 25 AD patients (85). In the same

Table 2. Different EEG analysis techniques motivated by dynamical systems theory show variable complexity measures across studies in AD

Measured parameter	Measured change	Study and number of patients included
Correlation dimension (D2)	Global decrease, increase in higher frequency bands, decrease in lower frequency bands	Yagyu et al. (74), n=21 AD- 29 MCI patients van Walsum et al. (77), n=20 AD patients Yoshimura et al. (78), n=17 AD patients
Omega complexity (OC)	Global increase	Yoshimura et al. (78), n=17 AD patients Czigler et al. (79), n=12 AD patients
Global complexity (GC)	Global decrease	Besthorn et al. (84), n=50 AD patients
Multiscale entropy (MSE)	Increase in higher frequency bands, decrease in lower frequency bands	Park et al. (81), n=26 AD- 22 MCI patients Escudero et al. (80), n=11 AD patients
Dynamical complexity (DC)	Global decrease	Ikawa et al. (85), n=25 AD patients

While studies with spectral and other non-DST methods involve relatively large number of subjects, studies with non-linear methods are limited, recruit remarkably lower number of AD patients and show inconclusive results. DST methods might be useful for the early recognition of MCI; however, combination with other methods is recommended.

study a correlation has been found also between verbal memory performance and DC values at post-temporal, left-central and parietal regions. Interestingly, in the early phases of AD, increased predictability and reduced complexity are predominantly visible in frontal and temporal areas (76).

Using the relatively new measures of mutual information (MI) and synchronization likelihood (SL), it has been demonstrated that the interdependency between the distant electrodes, especially between the frontal and temporal regions, between the frontal and parietal and between the hemispheres are reduced (26). Significant decrease in the SL of beta and high alpha band was also indicated in the study of Stam with 24 AD patients, where SL of both frequency bands had a strong correlation to the MMSE scores (86), while the gamma band was not affected. Babiloni and his colleagues obtained similar results in MCI; namely they found reduced SL in the delta band in 109 AD and 88 MCI patients with fronto-parietal dominance (87). Phase lag index (PLI) measurements revealed frequency dependent results in 18 AD patients; in the theta band patients showed higher whole-brain PLI and in the alpha band lower whole-brain PLI compared to patients with subjective cognitive decline (88). Concluded minimum spanning trees (MSTs) analysis from PLI suggested that global efficiency loss was defined mostly by the parietal and occipital loss of network organization (89).

Overall, results suggest that earlier alterations in neural dynamics can be identified with spectral analysis methods which can identify more precisely the early stages of Alzheimer (75). However, the combination of spectral and state-space methods proved to be highly sensitive in the early recognition of cognitive decline (62).

New methods derived from the mathematical framework of graph theory have recently become

popular in EEG analysis. Graph theory is used to describe network connectivity from EEG data. Nodes in the network often correspond to electrodes, and some measures of connectivity between electrode pairs are used to characterize edges (90). The nodes which receive more inputs and have more connections are referred to as hubs. Human cognition seems to be strongly related to the efficacy of the integration of different brain nodes. The normal human large-scale functional connectivity network can be described as a small-world network, with numerous local connections between adjacent nodes and a few but prominent connections between distant regions, which together lend high clustering and short path lengths to the network (91). Recent studies revealed that small-world like network properties of are replaced by random-world characteristics in AD. Studies demonstrated that AD patients (n=18) have a prominent decrease in the characteristic path length, degree correlation and mean clustering coefficient of delta and gamma band activity indicating severe loss in the local and global connectivity parameters (86,90). These findings were corroborated by MEG and fMRI studies as well including 18 (92), 20 (93), 21 (94) and 14 AD patients (95).

In summary, current EEG network analysis methods provide a promising new strategy for the diagnosis of AD and studying disease progression, and open a fresh view to cognitive decline from a network based perspective. State-space approaches seem to be also promising tools for the early recognition of MCI, especially when combined with spectral methods (Table 2).

3.3. Sleep-EEG studies in AD

Major neurocognitive disorders including Alzheimer’s disease as well as MCI are characterized with disturbed sleep. Growing evidence suggests that sleep disturbances precede the clinical onset

of cognitive decline in AD by years. A sleep-wake disturbance of clinical importance is found in up to half of the patients with dementia, and sun-down agitation is a frequent cause of institutionalization of demented patients (96). The circadian rhythm of dementia patients is disturbed with daytime sleepiness and disrupted night sleep. Whereas sleep changes may be severe in several types of dementia, a clinically significant sleep disorder usually develops only in the late phase of Alzheimer's disease (97-98).

Sleep transforms in many ways during healthy aging. Changes include reduction in the proportion of slow wave sleep (SWS) and sleep slow wave activity (SWA), the number and amplitude of sleep spindles as well as the density of rapid eye movements (REM) and the amplitude of circadian rhythms. With MCI there are further reductions of these parameters and all deteriorate further with the conversion to AD (99). Progressive changes in the quality, architecture and neural regulation of sleep may contribute to cognitive decline (100). The sleep profiles of patients with dementia of diffuse Lewy body and AD are different; which may have diagnostic importance (101).

Sleep pathology appears to be essential component of AD pathophysiology. Noticeably, sleep deprivation compromises cognitive and executive functions such as memory, attention, and response inhibition. In mice studies sleep deprivation impaired the mice's long-term and remote memory, even a month after the sleep deprivation session (102). The negative impact of sleep loss on memory has also been shown in patients with sleep disorders. Impairments of sleep-dependent memory consolidation for verbal and visual declarative information were found in patients with primary insomnia, for verbal declarative information in patients with obstructive sleep apnea, and for visual procedural skills in patients with narcolepsy-cataplexy (103). Conversely, increasing the amount of SWS and SWA by an anti-inflammatory agent in healthy humans improved memory consolidation (104). The positive cognitive effect of sleep slow waves was also shown in a transcranial slow oscillatory stimulation study where stimulation was applied during the afternoon naps of elderly individuals. The transcranial stimulation considerably increased frontal SWA significantly improving visual memory retention after sleep, but not retention in the location memory subtask and in the verbal memory task (105).

Changes in sleep microstructure have been observed as well in AD. Several studies have identified two types of sleep spindles: fast (13–15 Hz) centro-parietal and slow (11–13 Hz) frontal spindles. AD and MCI patients have shown a significant decrease in parietal fast spindle density, which positively correlated with their loss in MMSE scores (106). Fast spindles are involved memory consolidation as enhancing

sleep spindles with non-invasive brain stimulation in humans was found to significantly improve motor memory consolidation which correlated with the stimulation-induced increase of fast spindle activity (107). The impact of both slow and fast spindles on re-presentation learning has been shown in an odor re-exposure experiment (108).

Increased cerebrospinal fluid orexin levels were found causing sleep deterioration, which appeared to be associated with cognitive decline (109). The orexinergic system may be dysregulated in AD, while the role of orexin in memory function has remained controversial (110). Mice-experiments have shown an association of the amyloid-beta (A β) peptide and mitochondrial dysfunction, supporting a primary role for mitochondrial A β in AD pathology. Mitochondrial A β peptide levels were strongly negatively associated to the scores of cognitive tasks in an AD transgenic mice model experiment, indicating that amyloid could compromise the cognitive functions via the altered the mitochondrial signaling system. The degree of cognitive impairment in AD transgenic mice can be linked to the extent of synaptic mitochondrial dysfunction and mitochondrial A β peptide levels, suggesting that a mitochondrial signaling cascade induced by A β may contribute to cognitive impairment (111). Further, chronic sleep deprivation caused mitochondrial dysfunction in the frontal cortex of mice and a significant mitochondria-related A β increase in this cortical region suggesting that chronic sleep deprivation-induced mitochondrial dysfunction might be related to frontal mitochondria-related A β accumulation, preceding A β deposition in any other frontal cortical regions (112). These findings and the strong link of sleep-disruption in AD indicate a strong link between AD and sleep (113). It has been shown that insufficient sleep facilitates the accumulation of A β (114), potentially triggering earlier cognitive decline and conversion to AD (115). The sleep-wake cycle influences brain A β levels, and sleep deprivation increases the concentration of soluble A β leading to its accumulation, whereas sleep extension has the opposite effect (116). Furthermore, A β accumulation leads to increased wakefulness. Individuals with still normal cognitive functions and early A β deposition, report sleep abnormalities, similarly to mild dementia patients with incipient AD. Thus, sleep deprivation and AD may mutually amplify each other (117–118).

fMRI results suggest that the mechanism of the decline in short-term memory observed after acute sleep restriction is linked to the disruption of hippocampal-cortical connectivity (119). Age-related medial prefrontal cortex grey matter atrophy was associated with reduced non-REM SWA in older adults, correlating with the degree of the impairment of sleep-dependent memory retention. This memory impairment was associated with persistent

hippocampal activation and reduced task-related hippocampal-prefrontal cortex functional connectivity, potentially causing compromised hippocampal-neocortical memory consolidation. Thus it seems that the age-related medial prefrontal cortex atrophy diminishes SWA, resulting in impaired long-term memory (120). In a human and monkey neocortical microelectrode array study, the state of SWS was associated with the highest coherence values in beta and gamma bands across the width of the neocortex, supporting the idea of the SWS-related memory consolidation (121). A β -burden in the medial prefrontal cortex correlates with the impairment in non-REM SWA generation, which in turn is associated with sleep memory consolidation deficits during hippocampal-neocortical memory transfer. The association of the medial prefrontal cortex A β pathology with a deficit in hippocampus-dependent memory consolidation was indirect as it depended on the intermediary factor of decreased non-REM SWA. These findings suggest that amyloid deposition could compromise the sleep-dependent memory consolidation via the disruption of the SWS (120).

In summary, changes in macrostructural parameters of sleep EEG indicate that alterations in sleep are prominent and early features of AD. However, further studies are required to examine the microstructural features including the sleep spindles, K-complexes, cyclic alternating patterns and high frequency oscillations. These microstructural features might reveal novel aspects of AD-related memory impairment and open new ways to understand how amyloid and tau could lead to cognitive decline (Figure 1).

3.4. Event related potential (ERP) studies in AD

ERPs are electrical potential generated by the brain time-locked to a sensory, cognitive, or motor event (123124) and originate from summed excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs, respectively) produced by synchronous firing of a large number of cortical pyramidal neurons with similar spatial orientation (125). The ERP technique usually involves averaging brain responses over a large number of experimental trials to increase signal-to-noise ratio. The resulting waveforms are informative about the time course of sensory and cognitive processes with high temporal resolution and provide coarse spatial information about the location of the generating structures. ERPs allow us to study neural correlates of information processing including sensory-motor and perceptual processes as well as higher cognitive operations such as decision making. Furthermore, ERPs provide safe, noninvasive, easily accessible and cost-effective (126) readouts of synaptic neurotransmission which potentially make ERPs an ideal tool to assess cognitive processes in AD. In contrast to neuropsychological tests ERPs are

not influenced heavily by cultural background and educational level (127). As discussed above, there is a consensus in the field about AD being primary a disorder of synaptic plasticity (128). Given that ERPs are generated mainly by summated EPSPs and IPSPs, they may provide an ideal tool to probe synaptic dysfunction (129). In this section, we present an overview of the major ERP components and their relevance in Alzheimer type dementia.

Early ERPs (P50, N100 and P200) peaking roughly within two hundred milliseconds after stimulus onset are considered exogenous sensory components representing sensory processes as they depend mainly on the physical parameters of the stimulus, nevertheless they have been associated with attention as well (130). Although the prevailing view is that early ERP components are mostly unaffected, and therefore they are not ideal biomarkers in AD (131), a genetic study by Golob et al. showed significantly longer latencies for the N100, P200 components among familial AD (FAD) mutation carriers (132). Moreover reduced N100 amplitude was found in patients with sporadic or familial AD (133–135) and other abnormalities, including delayed latency of the P200 component have also been reported (136–137) indicating that early sensory-cognitive processes might be compromised in AD.

The N170 is a visual ERP component that is widely used in face perception research (e.g. 138). N170 amplitude is generally reported to be larger and more right-lateralized in response to faces than to other objects (139). A decrease in N170 amplitude has been reported in patients with AD (140–141). Although in a recent study Scheffer et al. found no differences in N170 amplitude between neurotypical controls and aMCI patients, they have found a delayed N170 latency in the MCI group (142) which is in line with compromised face processing in AD (143).

The N200 is a scalp negative waveform, which is evoked approximately 200ms after stimulus presentation. N200 is elicited by a novel infrequent stimulus during an oddball paradigm (usually investigated together with P300 component), and generated in fronto-central cortical areas (144). N200 is the earliest ERP that differentiates between target and non-target events, and it behaves functionally similar as the P300 wave. The N200 component is thought to represent automatic cognitive processes, such as pre-attentive stimulus evaluation and discrimination and is affected by stimulus probability. The N200 is sometimes further partitioned into three distinct subcomponents: the N2a, N2b, and N2c waves. The N2a is often referred to as mismatch negativity (MMN) component which we further discuss in the next section. In general, the N200 is sensitive to normal aging, as decreased amplitude and prolonged latency

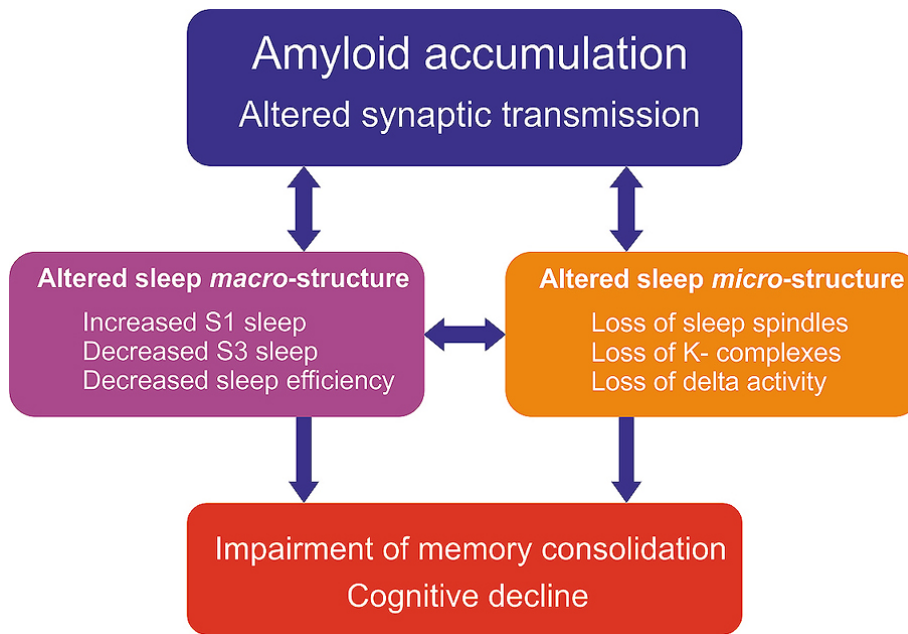


Figure 1. The multiple vicious circles of sleep loss and cognitive decline. Amyloid accumulation is the earliest and most prominent pathological hallmark of AD. Amyloid-induced synaptic transmission changes are well known from human and animal studies as well (6). Therefore, amyloid deposition is associated with altered sleep macro- and microstructure as well (122). The presence of amyloid seems to have a direct effect on sleep regulation leading to changes in the general sleep macrostructure (fragmented and superficial sleep, loss of slow-wave sleep) (99–101). Microstructural changes have been demonstrated as well (106) including decreased sleep delta power and diminished sleep spindles and K-complexes. Since these elements are essential for memory consolidation (108), cognitive functions are thought to be compromised directly by altered sleep and indirectly through to the impaired amyloid clearance mechanisms (122). There might be a bidirectional link between amyloid deposition and sleep fragmentation; impaired sleep might lead to increased amyloid burden (114–116), while amyloid accumulation compromises sleep regulation leading to altered macro- and microstructure (117–118).

is observed with age (145). Although it has been less extensively studied in AD, a few prior studies (usually investigating P300 and N200 component together) have found delayed N200 latency in AD patients compared to healthy aging (127, 137). Moreover Howe et al. in a recently published meta-analysis of 16 studies also demonstrated severe prolongation of the N200 latency in patients with AD and MCI compared to normative aging (126). This alteration seems to appear in the early course of the disease, suggesting that N200 latency changes could reliably predict MC/early ADI, and the conversion from MCI to AD. The predictive value of N200 latency delay has been improved by its combination with other biomarkers, such as amyloid-b 42 or CSF cytochrome c and also by a novel N2-P3 inter-peak index reported by Papagiakakos et al. that incorporates alterations in N200 and P300 latencies and amplitudes into a single parameter (146–147). Latency changes in AD have been associated with deterioration in attention processing and short-term memory processing, stimulus evaluation, and also in stimulus discrimination (123, 148). Furthermore N200 amplitude was found to be more sensitive in the early stages of AD, than P300 latency (147). In addition, prolonged latency was also found among FAD mutation carriers (132) and according to Vaitkevicius and colleagues the N200 subcomponent is less influenced by cholinergic treatment compared to the P300 component, therefore it may reflect the progression

of AD more independently from cognitive-behavioral effects produced by cholinesterase inhibitors (ChEIs) (149). To conclude, alterations in latency of the N200 component might be sensitive enough to differentiate patients with MCI and early AD from healthy controls as well as to predict conversion from MCI to AD (126,147). Nevertheless, more research is required with larger samples to determine reference values for N200 latency and amplitude for the differentiation of AD and MCI.

The P300 component has the longest history in clinical applications and it is the most extensively used potential to study dementia and aging. It is an objective index of cognitive activities, and in particular memory and context updating processes. The P300 is a relatively large (10–20 μ V), scalp-positive ERP component that peaks around 250ms to 500 ms) elicited by auditory, visual, or somatosensory stimuli (150). The P300 is most often investigated using the so-called “oddball” paradigm where a train of frequent irrelevant (standard/nontarget) stimuli is interspersed with random infrequent task-relevant (target) stimuli that have to be detected, and with infrequent task-irrelevant distracter stimuli (novelty) (151). The two rare stimulus types elicit two different ERP components; the slightly earlier positive deflection called P3a is elicited by the distracter (task-irrelevant) stimulus followed by the later P3b subcomponent elicited by

the target (task-relevant) stimulus (152). The P3a has frontocentral scalp topography whereas the distribution of P3b is maximum over midline centroparietal electrode sites (153). Target-related responses are thought to be generated in the parietal cortex and the cingulate whereas novelty-related responses in the inferior parietal and prefrontal regions (154), which also reflects interactions between the frontal lobe and the hippocampus (152). Regarding neurotransmitter systems, P3a shows strong association to the frontal/dopaminergic circuits whereas P3b is linked to the parietal/norepinephrine pathways (152). P300 originates from a distributed network associated with attention and working memory processes. It is generally assumed that the P300 component reflects the completed encoding of stimulus information into working memory (155). The P3a (involved in automatic novelty detection) has been linked to attentional processes and presumed to be an electrophysiological correlate of the orientation, whereas the P3b (associated with voluntary target detection) appears to be related to working memory and context updating processes (156). P300 amplitude increases with lower probability and higher discriminability of targets, and it is influenced by stimulus probability and saliency as well as availability of attentional resources (157). P300 amplitude correlates with memory performance, in the cognitively unaffected biological children of AD patients smaller amplitudes are related to decreased brain activation and lower scores in cognitive tests (158). P300 latency generally increases with the complexity of the stimulus evaluation and decision processes demanded by the task and indicates the closure of stimulus processing (152) as well as response selection (159). It appears to be also correlated with the agility of mental functions, thus a lower P300 latency is associated with superior cognitive performance (160) and reaction times (161). P300 is relatively independent of physical characteristics of the sensory input (157). Furthermore, the amplitude, latency and scalp topography of the P300 are modulated by a variety of factors that also tend to influence cognition, such as age (162), learning (163), substance use (164), pharmacological interventions (165), exercise (150) and diseases, particularly mental illnesses (166). P300 is sensitive to normal aging, as its latency increases in a linear fashion with 1 to 2 msec/y (167). Its topography tends to shift frontally with age (161) and its amplitude is progressively decreasing (168).

In general, several previous studies consistently reported a prolonged P300 latency in AD patients compared to age-matched healthy controls (for review see 169). P300 latency has been highly correlated with the severity of cognitive deficits in AD. Its latency increases as cognitive abilities decrease (170); in particular it was found to be sensitive to deterioration of language, memory, and executive functions (171). Although the majority of P300 studies

in AD focused on its latency, changes in its amplitude have also been found (172). A meta-analysis and meta-regression by Hedges et al. in concluded that the amplitude of the P300 component after an auditory or visual oddball stimulus was also significantly lower in probable Alzheimer's disease than in healthy controls (173). Moreover several recently published studies showed sensitivity and specificity above 80% (174). Studies that have differentiated between P3a and P3b latencies, reported more prolonged P3a latency in AD (126, 174). Also prolonged P300 latency has been reported in patients with MCI compared to healthy controls, and shortened P300 latency when compared to patients with AD. Two recent meta-analyses of these findings reported strong evidence that P300 latency can reliably differentiate between groups of MCI patients and controls (126, 175). Moreover Jiang et al. showed shorter P300 latency and larger amplitude in stable MCI patients compared to AD converters, and they suggested that P300 measures can predict MCI progression to AD (175). Furthermore, delayed P300 latency has been associated to positive cognitive response during cholinesterase inhibitor (ChEI) administration (131, 149). P300 latency has followed the same dynamics as the cognitive functions: initial improvement after 3 months of treatment, plateau phase of several months, and the gradual decrease after 6–12 months and later (150). The pre- and post-treatment latency differences were also correlated with cognitive ability and memory performance (131, 170, 176–177). Increased P300 amplitudes were found among normal subjects with first degree relatives of autopsy confirmed AD cases (178). An association has been revealed with genetic mutations, P300 latency of subjects carrying the apolipoprotein E (APOE) 4 allele (E4+) and with a positive family history of AD has been significantly longer than those of negative family history (155, 173–179). Furthermore, familial AD mutation carriers had significantly longer P300 latencies, which, together with other ERP abnormalities appear approximately 10 years before dementia manifestation (132). P300 changes have been shown to be positively correlated with neuropsychological test scores used in AD, such as the Trail Making Test Part B (TMT-B), the Wechsler Memory Scale, and digit span test that assess executive and working memory functioning. Furthermore Lai et al. suggested that P300 latency might be even a more sensitive index of cognitive decline than neuropsychological testing according to a longitudinal follow-up study in AD (170). Regarding variations in oddball protocols, a recent review of P300 studies in AD concluded that while the P300 assessment methodology is consistent across studies, the intensity, duration and type of stimuli, as well as the inter-stimulus interval and also the target-related task vary substantially among the studies (169).

In summary, P300 is associated with memory and cognition which are impaired in AD, which is in line

with the fact that presumed generator sites (centro-parietal cortex, frontal cortex, and hippocampus) are usually also affected in AD. P300 latency and also amplitude abnormalities have been suggested as sensitive tools to detect cognitive decline in patients with AD. P300 changes appeared to be objective and sensitive measures for discriminating subjects with MCI from controls and AD patients; moreover changes in P300 might be useful in the detection of the transition from MCI to AD. Furthermore, genetic studies found P300 abnormalities even in preclinical AD while subjects are in an asymptomatic stage. Pharmacological studies indicate the P300 latency could also be useful in quantifying the effect of the central nervous system's (CNS) response to medication.

Deviations in congruency expectations about meaningful stimuli such as words elicit the N400 event related potential which has been widely used as an index of lexical and semantic processing (180). Deficits in language and semantic integrative processes are known to be characteristics of AD (181), therefore the N400 might be a promising candidate to study this type of dementia. N400 is a negative-going potential peaking between about 250–550 ms) with maximal distribution over the centro-parietal electrode sites, although distribution can vary across protocols depending on the nature of the eliciting stimulus. Its amplitude can range from -5 to 5 μV (182). Studies using invasive electrophysiology and magnetoencephalography localized N400 generators in the temporal, parietal and the prefrontal cortical regions (180, 183). The N400 effect is usually calculated by contrasting responses to congruent and incongruent stimuli to reveal the ERP component related the investigated experimental variable (182).

Semantic priming and repetition priming have been used widely to examine semantic memory functions in AD (175). Semantic priming (SP) facilitates retrieval of target words that are preceded by contextually related priming words compared to words in unrelated context (184). The N400 is sensitive to semantic congruity, and its amplitude is positively correlated with semantic processing load and negatively correlated with semantic expectancy. Thus semantically incongruous (inappropriate or unexpected) stimuli elicit larger responses compared congruous stimuli (185), frequently described as N400 effect. As it is generally assumed, N400 SP effect represents a more prominent signal processing need on neural resources for unexpected stimuli relative to the expected ones (182). Other repetition priming effects are reviewed later in the P600 section.

The N400 component as well as the N400 SP effect was found to be smaller and delayed in the elderly (186) indicating that the N400 is affected in

normal aging. Nevertheless, the majority of studies investigating N400 effects based on manipulations of semantic congruity in AD consistently revealed reduced N400 amplitudes or slower latencies compared to elderly controls (187). Moreover, different topographic N400 congruity effects have been shown in AD patients (188). Reduced N400 semantic congruity effect in AD patients relative to controls was found to sentence-terminal words of visual (189) or auditory (190) sentences, to visual words congruous/incongruous to the preceding category (191), to semantically related/unrelated line drawings and pictures (192), as well as to picture primes followed by visual word targets (193) or to visual words followed by picture targets (188). In contrast to the aforementioned findings, other studies reported normal N400 congruity effect in mild AD suggesting a relatively preserved semantic memory (189). However, in a recent study using an ERP paradigm optimized for AD corroborated the aforementioned positive results and found decreased N400 amplitudes among MCI/early AD patients compared to normal controls (76, 135). Furthermore studies investigating the word-repetition effect also showed significant attenuation of the N400 effect and an additional atypical anterior N400 distribution in patients with AD compared with controls (135). Nevertheless, the authors observed a typically shaped N400; hence they suggested preserved semantic knowledge but impaired access in AD (Word repetition effect is further discussed in the P600 section.) MCI patients also tend to show delayed N400 latencies, reduced N400 semantic congruity and word repetition effect compared to healthy elderly subjects (194). Olichney et al. have shown in a longitudinal study that MCI converters had abnormal N400 effects (loss of both the N400 repetition effect and N400 congruity effect), which were present at year 1, and became pronounced by year 2. Moreover an abnormal N400 (or P600) effect was associated with an increased risk of transition from MCI to AD. They also found an atypically anterior N400 distribution in MCI converters, similar to mild AD (129). Abnormal N400 topography was found by Grieder et al. to be associated with decreased anterior temporal cerebral blood flow (possibly reflecting the underlying pathology), and they suggested that N400-topography alterations might be a potential biomarker for the detection of early dementia (195). Furthermore, according to Bobes et al., deviant N400 topographies might occur even before the manifestation of semantic memory symptoms. They reported abnormal parietal distribution of N400 congruity effect among asymptomatic carriers of E280A PS-1 mutation (196).

In sum, altered N400 semantic congruity effect in AD likely reflects the well-known dysfunction of semantic memory processes in AD (181). Abnormalities of N400 (reduced N400 effect and altered topography) have been consistently found in previously published studies of mild AD and MCI and

they seem to be related to the anterior temporal lobe, a predilection site for AD pathology (38). Abnormalities of the N400 effect (including both semantic congruity and word repetition effect) may offer sensitive markers for detecting and monitoring the stages of disease progression in very early AD and for the subsequent transition from MCI to AD. Moreover deficits of N400 effects in cognitively normal elderly persons may be an important sign of preclinical AD.

The P600 or Late Positive Component (LPC) has been suggested as an index of memory encoding and retrieval processes, including episodic and declarative memory (129). The P600 component is a large late positive waveform, with a centro-posterior distribution, which reaches its peak around 600 milliseconds after stimulus presentation. Intracranial studies concluded that putative P600 generators include several paralimbic cortical regions (cingulate, orbito-frontal cortex and temporal pole), the medial temporal lobe (MTL) including the hippocampus and entorhinal cortex, and further multi-modal association neocortical regions (ventrolateral prefrontal, lateral temporal cortex). Depth recordings in several paralimbic and association neocortical regions have shown biphasic ERP components which resemble the N400–P600, suggesting a link between these components (197). Studies in dementia focusing on the P600 have mainly used repetition priming to probe memory processes.

Behavioral effects of repetition priming typically include improvements in response speed or accuracy to repeatedly presented stimuli (198). Both the N400 and P600 can be reliably elicited and modulated using a word repetition paradigm. In word list recognition experiments recognized/remembered words that go through a more extensive encoding process evoke larger late positivity (199). In contrast, preceding semantic contexts which increase the probability of a word's repeated occurrence have the opposite effect (200). While diminished N400 repetition effects have been linked with abnormal semantic/conceptual priming (201), P600 priming effects have been associated with episodic verbal memory and declarative memory skills (192).

Prior studies of ERP word repetition effects in AD have reported inconclusive results (202–204). However, Olinchey et al. used a semantic categorization task in a word repetition paradigm that manipulated semantic congruity and repetition. ERPs obtained in their paradigm showed high sensitivity and specificity (100% and 80%, respectively) to AD. They consistently have found reduced or absent P600 and N400 word repetition effects as well as atypical anterior N400 distribution in patients with AD compared to controls (135, 200). Using the same word repetition paradigm in an fMRI study they have found left hemisphere dominant

repetition effects in medial temporal, prefrontal and parietal networks associated with both encoding and retrieval of episodic memory (205).

The aforementioned research group has also demonstrated reduced P600 word repetition effects in patients with MCI (195). Furthermore, reductions in either the P600 or N400 word repetition effect in MCI patients were associated with greater likelihood for conversion to AD dementia (129). Olinchey and colleagues used an incidental verbal learning paradigm with high sensitivity to prodromal AD in seven elderly subjects, who had normal cognition at the time of ERP recordings but showed subsequent cognitive deterioration or had AD pathology confirmed by autopsy. A reduced P600 repetition effect was found compared to normal elderly controls. The P600 effect was severally compromised even in patients with minimal neurofibrillary pathology, and the authors suggested that amyloid deposits might disrupt effective communication within the network of neural generators underlying the P600 response (206).

In conclusion, progressive alteration of the P600 effect may be a manifestation of failing P600 generators, which may relate to the early involvement of the medial temporal lobe. The MTL (anterior fusiform, parahippocampal gyrus, hippocampus) is known to be involved in the early neuropathology of AD; deficits in the episodic memory are usually the earliest symptoms. ERP word repetition effects appear to be very sensitive to AD and MCI. P600 and N400 repetition effects have consistently been found diminished in AD which may be linked to semantic and memory impairments. Decreased P600 and N400 repetition effects appear to be useful biomarkers for predicting conversion from MCI to AD dementia, thus altered P600 effects in elderly with normal cognition could be a red flag for preclinical AD.

The emerging picture after overviewing the abnormalities of cognitive ERPs in AD shows that early, sensory-evoked potentials are usually found to be less affected in AD, although the results are not entirely conclusive. Later potentials reflecting higher cognitive processes, such as the P300 component, could be more effective for detecting the progression of cognitive decline and attention deficits, thus it could prove to be a useful biomarker in CNS drug development. A decreased P600 and N400 repetition effect and also a delayed N200 latency can be detected consistently in the early stage of the disease therefore they could reliably predict the conversion from MCI to AD. Interestingly, genetic and longitudinal studies also found the abnormalities of several ERP components (N200, P300, N400, and P600) in the pre-symptomatic stage of AD. ERP abnormalities are not specific to Alzheimer's disease; they have been also documented in several other neuro-psychiatric disorders. The sensitivity

Table 3. Changes in amplitude and latency of different ERP components in AD, MCI and preclinical stages of AD

ERP component	Amplitude in AD	Latency in AD	Amplitude in MCI	Amplitude in preclinical AD	Effect of cholinergic treatment
Early ERPs	IC	IC	DNA	DNA	DNA
N170	↓ / IC	↑	DNA	DNA	DNA
N200	↓	↑↑	↑	↑	Less influenced by cholinergic treatment
P300	↓↓↓	↑↑↑	↑↑↑	↑↑	Response to cholinergic treatment
N400	↓↓	↑↑	↑↑	↑	DNA
P600	↓↓	↑↑	↑↑	↑	DNA

The number of arrows indicates the number of studies reporting concordant results: ↑ = 1–5 studies ↑↑ = 5–10 studies ↑↑↑ >10 studies. DNA = Data not available; IC = inconclusive results.

and specificity of ERP measurements showed great variability in the literature; therefore the diagnostic validity of these measurements seemed to be poor. However, recently several studies using promising clinical ERP approaches presented prediction accuracies of MCI/AD progression in the 85–95% range (129, 207–208). The separation of subcomponents (174) and also the additional use of two or more components of the event-related potentials (147, 208), the combination of ERP measurements with event-related synchronization (ERS) measurements (136) or with neuropsychological tests has been found to be useful to increase sensitivity and specificity (165) and thus improve reliability of the overall test procedure. Furthermore the importance of the use of carefully designed paradigms with higher sensitivity to AD (137, 199), MCI (194) or even to prodromal AD (206) has been highlighted (Table 3).

3.5. Mismatch-negativity (MMN) studies in AD and MCI

The mismatch negativity (MMN) is an ERP component generated automatically in response to events that deviate from what is likely to happen. A commonly used experimental protocol to elicit MMN is the oddball paradigm (209), where frequent, standard stimuli are interspersed with rare, deviant stimuli. The MMN component is usually obtained by subtracting the ERPs to standards from those to deviant stimuli. Although MMN can be elicited by stimuli in virtually all sensory modalities, auditory and visual paradigms have been used most frequently. Automatically detecting a change in the sensory input works not only at the level of simple acoustic or visual features, but also at higher, more abstract stimulus attributes (209). The MMN has been proposed to reflect the automatic functioning of a “primitive intelligence” (210), which generate predictions about future events by extracting invariant patterns from the varying environmental sensory input even when they are task-irrelevant. Extracting such regularities (211) in the absence of attention corresponds to implicitly keeping track of statistical probabilities of sensory events (212) that

allows detecting improbable events; the mismatch between predicted and observed stimuli is thought to be signaled by the MMN response, thus it is increasingly considered as a perceptual prediction error signal (203–219). Since such signals play a fundamental role in veridical sensory and cognitive processes, the MMN component is a suitable candidate as a marker of cognitive decline.

3.5.1. MMN in AD

According to the guideline for the diagnosis and management of Alzheimer’s disease by the European Federation of the Neurological Societies (EFNS), spectral EEG markers based on oscillatory power alterations in different frequency bands may help to differentiate between AD, subjective complaints and psychiatric diagnoses (220). However, ERPs are currently not listed in the guideline. ERPs or MMN in particular, to qualify as a clinical marker, should have a sufficiently high sensitivity for detecting early AD, as well as a sufficiently high specificity for distinguishing it from other neurodegenerative disorders. Furthermore, according to the Consensus Report of the Working Group on Molecular and Biochemical Markers of AD (221) by the Ronald and Nancy Reagan Research Institute, an ideal marker should be non-invasive, simple to perform, and inexpensive. However, currently only diagnostic approaches based on cerebrospinal fluid-tau and positron emission tomography (PET) approaches demonstrated sensitivity as well as specificity in the range of about 70%-100% (222). Clearly, markers obtained with these methods do not fulfill the above ideal requirements of non-invasiveness and cost-effectiveness. Regarding biomarkers for disease progression, a recent systematic review by McGhee et al. (223) found that the most commonly studied marker was brain MRI, whereas electrophysiological studies made up only a small fraction of the included studies. They found that studies were generally of poor quality, underpowered due to relatively small number of participants, and had flawed methodologies, indicating that the field in general

needs to adopt stricter methodological guidelines. The authors concluded that there was insufficient evidence to recommend any biomarker as an outcome measure for disease progression in Alzheimer's disease (223) and recommended a "roadmap" for future studies.

Earlier reviews on electrophysiological biomarkers, including MMN, were optimistic and suggested that ERP components may serve as clinically useful, objective, noninvasive, economic and reliable method for assessing neurological disorders, including AD (130, 224). The first auditory MMN study (225) that used duration deviants in AD patients (n=9) reported that MMN amplitude decreased more in the patients than in the age-matched controls, and suggested that the memory trace reflected by the MMN response decays faster in the AD patients. In a subsequent magnetoencephalography (MEG) study by Pekkonen et al. (226) that used a similar oddball paradigm, AD patients (n=22) had significantly delayed N100m responses in the left hemisphere that correlated with the impairment of language functions. Unfortunately MMN was not investigated due to constraints on the recording time in the study. Kazmerski et al. (227) used both an active and a passive oddball paradigm in probable AD patients (n=16), age-matched and young controls. They found a decreased MMN both in AD patients and older controls during both active and passive oddball paradigms, although reliably MMN amplitude differences were observed primarily during the active oddball sequences. In general, the AD group showed reduced MMN amplitudes relative to the older controls, although these differences were not always statistically reliable. Gaeta et al. (228) systematically varied stimulus deviance to study whether the mechanism underlying the MMN can track wide differences in the physical characteristics of auditory stimuli. They found that patients with mild AD (n=8) showed robust MMN responses to the three types of deviant stimuli which did not differ in amplitude or latency from that of the old control group, and suggested that patients with mild AD have an intact sensory memory mechanism.

The robust effect of ageing on MMN has been shown in several studies in the auditory (229–230), visual (231–232), and somatosensory (233) modalities. A recent meta-analysis on the effects of physiological aging on MMN (234) concluded that an attenuated MMN to duration and frequency changes is a robust feature in healthy aged adults. Thus, the MMN, as a potential biomarker in AD, should be specific enough for differentiating the baseline effect of healthy aging from a putative AD-specific alteration of the MMN.

3.5.2. MMN in MCI

The transitional continuum between normal aging and dementia is referred to as MCI. There is a

considerable clinical and pathological heterogeneity in MCI (235), which precludes reliably predicting transition to AD (236). Furthermore, pathological studies (237) confirmed remarkable heterogeneity of AD subtypes and progression rates. Nevertheless, there is complex but predictable relationship between the severity of cortical pathology and the extent of cognitive impairment (238). At-risk individuals with MCI would particularly benefit from a biomarker at this early stage of AD as it would allow early detection before irreversible degeneration takes place and prevent progression to full AD. Indeed, differentiating between MCI, AD, and physiological ageing, as well as other forms of dementia is a central issue in more recent MMN studies. Mowszowski et al. (239) investigated auditory MMN and its relationship to neuropsychological performance in MCI individuals (n=28) and age-matched controls. Looking at MMN at temporal sites they found reduced responses in the MCI group. The reduced MMN at the right temporal site showed a relationship with poorer verbal learning, whereas reduced MMN at left temporal site was associated with increased disability. The authors suggested MMN may be a viable neurophysiological biomarker in the at-risk MCI group, however they failed to correct for multiple comparisons in their correlation statistics. A recent longitudinal study (240) used auditory MMN in a cohort of MCI individuals. At the first time point n=26, at the follow-up n=7 MCI patients were included in the analysis. The two evaluations were separated by an interval of 1.5–2 years. At the first time point, significant group differences were observed only in the 50–64 years age range, but not in the >65 years range. At the second time point only one age range (62–89 years) was studied. The MMN amplitude was reduced in the MCI compared to the control group in both evaluations, although significant group differences were not present between MCI and control adults in the >65 years range.

Ji et al. (241) used auditory MMN to compare automatic change detection in amnesic MCI individuals (n=43) and age-matched controls. Both MMN amplitude and latency were analyzed. Results showed that while amplitudes did not differ between the two groups, the latency of the MMN component was significantly delayed in the aMCI adults. Although no other clinical test groups were included in the study, the authors concluded that MMN latency appeared to be a sensitive and specific biomarker of MCI. A high-density EEG-3D vector field tomography approach was used by Papadaniil et al. (242) to investigate auditory MMN in MCI (n=21) and AD patients (n=21) as well as healthy elderly controls at the scalp and at the source level. Analysis of MMN amplitude and latency at the scalp showed significantly delayed response in the AD group compared to the healthy elderly. Source reconstruction revealed curiously similar activation patterns for the MMN and the P300 component. Several

MMN-related activations were found to be significantly different across the groups; however statistical tests were not corrected for multiple comparisons, making interpretation of the results difficult. The authors concluded that alterations of MMN might serve to create biomarkers of dementia and its progression. Three groups of subjects were investigated by Idrizbegovic et al. (243) using auditory MMN. Patients with AD (n=32), MCI (n=44), and patients with subjective memory complaints without cognitive decline (SMC, n=27) were included. Stimulus was presented monaurally, separately to the right and left ears. The MMN in the left ear condition was significantly smaller in the AD compared to the MCI group. Furthermore, a left ear advantage (LEA) of MMN was observed in the MCI and SMC groups, which was absent in AD group, however the LEA was not systematically tested across the groups. The authors speculatively concluded that the absence of MMN asymmetry in AD might be related to a dysfunction to register changes in tonal stimuli. Another study that used auditory MMN as an index of cognitive decline included a final sample of amnesic MCI (n=8) and AD patients (n=12), as well as age-matched controls (244). MMN was elicited with shorter and longer inter-trial intervals (ITI), and was measured at frontal and temporal sites. Results showed that at short ITI, in MCI and AD patients MMN was only found at temporal sites, whereas in healthy elderly it was present at both frontal and temporal sites. At longer ITI, MMN was absent in the patient groups, only healthy controls showed a reliable MMN response at temporal sites. Unfortunately it is not clear from the results whether the lack of a significant MMN response in the patients corresponds to a reliable difference in MMN between the control and any of the patient groups. Significant correlations were found between MMN amplitude and neuropsychological test scores; however the statistics were not corrected for multiple comparisons. The authors suggested that the auditory MMN might be adopted as a marker for cognitive decline in pathological ageing.

MMN in the visual modality has also been used to differentiate between healthy and pathological ageing. In a study in AD patients (n=8), age-matched and young adults Tales and Butler (245) found that while the visual MMN response had a relatively constant amplitude in the older controls, it was absent in the first experimental block and much larger in the second block. In a subsequent study (246) the same group investigated visual MMN in MCI (n=8) and AD (n=10) groups as well as age-matched controls. They found that both the MCI and AD patients showed a significantly increased vMMN in the 140–250 ms time window compared to healthy elderly. In this interval both the MCI and AD groups failed to show a significant vMMN in the first experimental block but exhibited a significant vMMN response in the second, showing the same pattern as in their previous study (245). However,

in a recent follow-up study (247) with a larger cohort of AD (n=20) and MCI (n=25) patients as well as healthy older controls no significant difference between AD patients and healthy older adults was found in vMMN amplitude. Results showed though that MCI patient had a reduced vMMN response compared to elderly controls. However, earlier ERP components such as P1 was reduced in AD patients, and N1 amplitude was attenuated in MCI and AD patients relative to controls, furthermore vMMN and lower P1 amplitudes showed a relationship with cognitive impairment scores. The authors concluded that visual evoked potentials and MMN may provide objective markers of cognitive decline.

The specificity of MMN to differentiate between neurodegenerative disorders has been tested in two studies. Brønneck et al. (248) compared auditory MMN responses in patients with dementia associated with Parkinson's disease (PDD, n=15), dementia with Lewy-bodies (DLB, n=17), AD (n=16), Parkinson's disease without dementia (PD, n=16) and healthy control subjects. Results showed that PDD patients had reduced MMN compared to the DLB, PD, and the HC groups, but did not differ significantly from the AD group. Another recent study (249) compared auditory MMN in patients with AD (n=15), bipolar disorder (n=25), schizophrenia (n=49), and healthy controls. Significant reduction in MMN amplitude was only observed in the schizophrenia group. Despite the relatively larger cognitive deficit in the AD group, the MMN findings showed intact sensory and cognitive processes.

3.5.3. Conclusions

The overwhelming majority of the studies reviewed here reported some MMN alterations in MCI and/or AD patients. However, different studies observed different alterations either in latency or amplitude, or at different scalp locations. Outcome variability is a serious issue which may relate to several factors. First, the small sample size in many studies renders their statistics underpowered. Effect size was often not communicated in the results, which makes comparisons between studies difficult. Larger samples would possibly allow to handle the issue of disease heterogeneity, i.e., by the identification of more consistent subgroups within the heterogeneous disease population. Second, studies differ to a large extent in their stimulation protocols, measurement parameters, and data analysis. Furthermore, some studies had presumably flawed methodologies, and apparently several studies had flawed statistical analyses. Other factors that might contribute to the outcome variability include the medication status of the participants which is very often ignored, together with other potentially useful covariates (e.g., cognitive reserve, demographics). Furthermore, the

overwhelming majority of the studies were cross-sectional, which has precluded later verification of the MCI status at the time of the study.

With regard to the issue of sample size, future studies would benefit from performing a power analysis to determine the required sample size to optimize the probability of detecting a true effect given a desired effect size. Regarding disease heterogeneity, the lack of longitudinal studies in the field clearly hinders the accurate evaluation of any MMN-based markers due to limited predictive accuracy of the MCI label. Furthermore, machine learning techniques that have been used on MRI data to discriminate subgroups in MCI patients (250) might be useful to define subgroups in the heterogeneous at-risk and disease populations. An optimal experimental protocol could be adopted to overcome excessive variation in measurement parameters and analysis across studies.

3.5.4. Future directions – Computational neurology

The majority of the studies reviewed here observed a change in the amplitude or latency of the MMN in MCI and AD patients. However, the sensitivity and specificity of these alterations in simple characteristics of the MMN response, such as amplitude or latency, are unlikely to be sufficient to qualify MMN as a biomarker in the early diagnosis of, or outcome predictor in AD (251). However, recent advances in computational neuroscience provide us with tools to investigate the population dynamics of the neuronal networks underlying ERPs. Dynamic causal modeling (DCM) studies revealed the dynamics of the functional network underlying the MMN component (213–214, 252). The development of computational tools that allow studying large-scale neuronal population dynamics has led to the emergence of a new field at the interface between neuroscience and psychiatry that aims to use computational methods to identify objective diagnostic assays, and to overcome issues arising from the enormous heterogeneity in spectrum diseases that are traditionally diagnosed according to subjective symptoms (253–254). The new discipline of computational psychiatry uses neurobiologically motivated formal models that describe brain function in computational or mathematical terms for elucidating mechanisms of pathophysiology that may inform both diagnosis and treatment (14, 255–256). For example, parameter estimates of network connectivity obtained from dynamic causal models of the auditory MMN have been successfully used to differentiate between patient populations and controls in vegetative state (257) and schizophrenia (258).

DCM of the MMN response is a promising tool to characterize glutamatergic dysfunction in schizophrenia (259) and it also might prove useful to

quantify cholinergic dysfunction in AD (260–261), as recently Moran et al. (262) demonstrated that DCM is feasible to characterize cholinergic effects on the MMN component, which was found to modulate gain in pyramidal cells in the auditory sensory cortex. Furthermore, recent DCM studies revealed that the observed attenuation of the MMN response in healthy ageing is likely due to alterations in forward connectivity within temporal (263) and/or between temporal and frontal regions (264). Thus, although an index of cognitive decline based on a simple amplitude measurement of the MMN is unlikely to yield sufficient sensitivity and specificity to qualify this ERP component as a biomarker, computational models of the MMN might allow effectively disentangling the factors of healthy aging and pathological alterations as they seem to affect the network underlying the MMN in different ways.

The example of MMN, one of the most studied cognitive brain potential, highlights that translating the advances in computational modeling tools of basic neuroscience to psychiatric and neurological population might allow us to tackle long-standing issues in these fields. By applying novel approaches to better understand disease mechanisms, we might abandon subjective symptom-based disease categories and dissect the currently heterogeneous clinical populations and spectrum disorders into subgroups defined instead based on alterations in neurobiological mechanisms. In this challenging mission at the interface of neuroscience and neurology (265), markers derived from spontaneous EEG, as well as sensory-cognitive brain responses such as MMN and other ERP components have the potential to contribute to the development of computational assays that might inform diagnosis and treatment, and track disease progression.

4. EEG IN THE DIFFERENTIAL DIAGNOSIS OF COGNITIVE DECLINE

The differential diagnosis of neurocognitive disorders may be difficult due to several diseases with overlapping clinical symptoms and the large inter-individual variability in the progression and manifestation of the disorders. Apparently the revolution of the neuroimaging techniques has significantly improved our diagnostic accuracy in neurodegenerative disorders. However, EEG/ERP methods might offer many, still unexploited benefits both in research and clinical areas. In this section we briefly overview the potentially useful EEG methods in the differential diagnosis of various dementia syndromes.

Frontotemporal dementia (FTD) that affects mainly the anterior temporal pole and the prefrontal cortex is responsible for 15% of cognitive deterioration

cases. In the early phase of the disease changing behavior and progressive speech difficulties dominate the clinical symptoms. Subsequent progression affects episodic memory functions as well. Differentiation from AD is frequently challenging, especially in the early stages, when FTD can mimic the symptoms of AD (266). An early study with pathologically confirmed FTD demonstrated that the EEG did not show specific changes when analyzed by visual inspection however a marginal elevation in theta power could be observed (267). Further studies also showed that visual inspection of the EEG demonstrated normal appearance compared to AD (268). In contrast, quantitative EEG methods revealed a significant decrease in spectral power of the alpha and beta band, while lower frequencies were unaffected (269). A recent global field power analysis (270) corroborated these prior findings. A LORETA study yielded similar results for the delta band but found no differences in the higher frequencies between FTD and AD patients (271). The major difference between AD and FTD seems to be the increased spectral power of delta and theta band in AD (272), while it remains unaffected in FTD according to most of the studies (269–271). Graph analysis also indicated a potentially distinctive measure; AD patients showed the features of random systems, while FTD patients presented changes towards a more ordered network (92). However, another study using a similar network analysis approach did not find any differences (268). PLI and MST analysis indicated that FTD patients present lower theta band whole-brain PLI and higher alpha band whole-brain PLI than AD patients, while MST indicated that frontal networks are selectively involved with a preserved global functional efficiency compared to AD where the global efficiency was significantly impaired by occipital and parietal network dysfunction (273). D_2 complexity was also reduced in FTD and the increase in eyes-opened condition was diminished compared to normal controls (274), similarly to the findings in AD. While there is a special genetic phenotype of FTD with parkinsonism and epileptic seizures (275), unfortunately only one study is available about the prevalence of epileptic seizures in FTD (276). It revealed seizures in 5% of FTD patients (276); in contrast, epileptiform EEG is frequently observed in AD (277).

Mood disorders such as major depression and anxiety disorders are frequent comorbidities of neurocognitive disorders. It is still unclear, whether late-life depression is a risk factor of AD or a prodrome of the disease (278). It is also well-known that depressive symptoms could mimic cognitive decline, therefore differential diagnosis of mood disorders and AD is necessary, however, it is often difficult. EEG is a useful tool to discriminate AD patients from late-life depression with a 70–85% reported accuracy (279). The major finding in depression studies is the elevated alpha and beta power, especially bilaterally

in the anterior regions (280). In coherence studies, the most consistent finding in patients living with depression is the reduced frontal interhemispheric coherence in all frequency bands (280–281). EEG complexity studies showed similar results in depression and AD, both diseases demonstrating a significant loss in interhemispheric coherence (282). Many functional connectivity studies indicated that patients with depression show increased connectivity, in short-connections of the left hemisphere and in long-associations of the right hemisphere (283). Thus, the major features that differentiate between AD and depression in EEG include the increase in fast frequencies, the unaffected low frequencies, the dominance of EEG changes of the frontal lobes and the generally elevated connectivity in depression.

Diffuse Lewy-body dementia (DLB) and Parkinson-dementia (PDD) are synucleinopathies showing typical motor phenomena, so the differentiation from AD is usually straightforward. However, visible symptoms that usually accompany impairments of the motor pathways are not present in each patient; in these cases EEG could serve as a useful diagnostic tool (284). EEG studies in DLB and PDD reported a decrease in alpha power and diffuse slowing could be demonstrated in both conditions (285). Interestingly, loss of alpha dominance and slowing could be more prominent in DLB compared to AD (286–287). Bilateral frontal intermittent rhythmic activity (FIRDA) is a common feature of EEG in DLB (288). Grand total EEG score (GTE) was able to distinguish AD from DLB with 72% sensitivity and 80% specificity (289). Increased dimensional complexity, higher entropy and nonlinearity were demonstrated in PD, while these parameters decreased in PDD (290–291). Stam et al. observed elevated L_1 in PD patients, but no data regarding PDD are available (292). In PDD, a decrease in functional connectivity was found with a similar pattern as in AD (293), while studies on non-demented PD patients reported increased alpha and beta band connectivity cortical areas as well as between the subthalamic nucleus and the motor cortex (294–295). In DLB, a reduction of global coherence in the alpha band emerges as a consistent finding (296), while studies on delta range are equivocal (297). It seems feasible that synucleinopathies show similar EEG patterns as AD when cognitive deterioration is already present which renders the usefulness of EEG in the differential diagnosis of AD and PDD/DLB questionable. Regarding the prevalence of epileptiform patterns in DLB and PDD, no data are available (298).

In summary, there are relatively few studies that investigated the utility of EEG/ERP in the differential diagnosis of neurocognitive disorders. The variability in methods and the lack of systematic replication studies offers a mosaic-like landscape of results that render synthesis difficult. Nevertheless,

Table 4. Potential utility of EEG markers in the differential diagnosis of cognitive decline

EEG feature	Alzheimer's disease	Frontotemporal dementia	Diffuse Lewy-body dementia	Depression-related cognitive decline
Delta-power	↑	x	↑	x
Theta-power	↑	x	↑	x
Alpha-power	↓	↓	↓	↑
Beta-power	↓	↓	↓	↑
Complexity	↓	↓	↓	↓
Connectivity	↓	↓	↓	↑
Epileptic activity	↑	↑	DNA	DNA

↑: increase, ↓: decrease, DNA: data not available. Across studies there are clear findings suggesting that most common forms of neurocognitive disorders show different EEG characteristics.

some promising findings suggest that EEG could be used to assist AD diagnosis and differentiate it from other forms of dementia. The major changes in spectral EEG characteristics that seem to be highly sensitive in the diagnosis of AD include attenuated power in higher frequency bands and increased power in lower (delta and theta) bands. Further potentially useful indices include altered network characteristics (graph analysis), decreased global connectivity, and the high prevalence of epileptiform discharges and epileptic seizures.

While in AD the most prominent changes include an increase in delta power and a decrease in alpha power (40–42), the lower frequency bands seem to be unaffected in FTD (269) and in depression-associated cognitive decline (280). Interestingly, regarding the alpha and beta frequency bands, spectral power show a consistent decrease in AD, FTD, and DLB, while there is evidence for increased power in these bands in depression-related cognitive decline (280). While complexity measures show a consistent decrease across all four diseases, connectivity in DLB (296), AD (80–81, 84) and FTD (274) share the same phenomenology (significant reduction) but depression shows increased connectivity (283). Data on the prevalence of cognitive-decline associated epileptic activity is limited but AD patients are more likely to develop epileptic seizures and epileptiform discharges (277) (Table 4).

5. CONCLUSIONS AND FUTURE PERSPECTIVES

EEG and ERPs allow noninvasive assessment of synaptic dysfunction with an extremely high temporal resolution (299). AD is suggested to be primarily a disorder of synaptic plasticity (128, 300). Furthermore altered synaptic plasticity was found prior to the appearance of Aβ containing plaques and brain atrophy in animal models (301). EEG and ERPs primarily reflect synaptic transmission processes, thus they seem to be particularly suitable for studying altered

synaptic plasticity. According to Olinchey and colleges ERPs could be even more sensitive to early alterations in AD than volumetric MRI (302). It is important to note that some studies reviewed here were of poor quality and underpowered due to relatively small sample sizes indicating a need to adopt stricter methodological standards. Nevertheless, our current review suggests that EEG/ERP-derived measures of neurotransmission definitely deserve further consideration as candidate biomarkers in AD, MCI and even preclinical AD. Figure 2 highlights a small set of promising findings reviewed here and areas of potential clinical applications of EEG/ERP measures in dementia research in general. Regarding further research, we suggest that studies are needed that evaluate as many as possible of the overviewed spectral markers and ERP components in a longitudinal setting, ideally from the pre-symptomatic stage with respect to their relative sensitivity and specificity. There is an urgent need to standardize ERP assessment procedures in order to obtain results that allow direct comparisons across different studies and laboratories. ERPs might provide robust, cost-effective, and easily accessible markers to help diagnosis, track disease progression, and evaluate response to therapy, thus standardized guidelines for ERP measurements in AD are warranted.

The pathologic changes of AD are generally deemed to start many years before the initial symptoms of cognitive deterioration and the clinical diagnosis of dementia (303). There is an urgent need to identify the disease in the prodromal or in the early clinical phases such as MCI. EEG and ERP methods in clinical neurophysiology might serve as important tools in the early diagnosis of cognitive dysfunction. These methods are easily accessible, non-invasive, relatively cheap, and provide objective assessment of synaptic neurotransmission underlying sensory and cognitive processes. However, although there are several promising results, it can be concluded that at the moment there is no clinical neurophysiological marker or protocol available that could provide a definitive diagnosis of dementia.

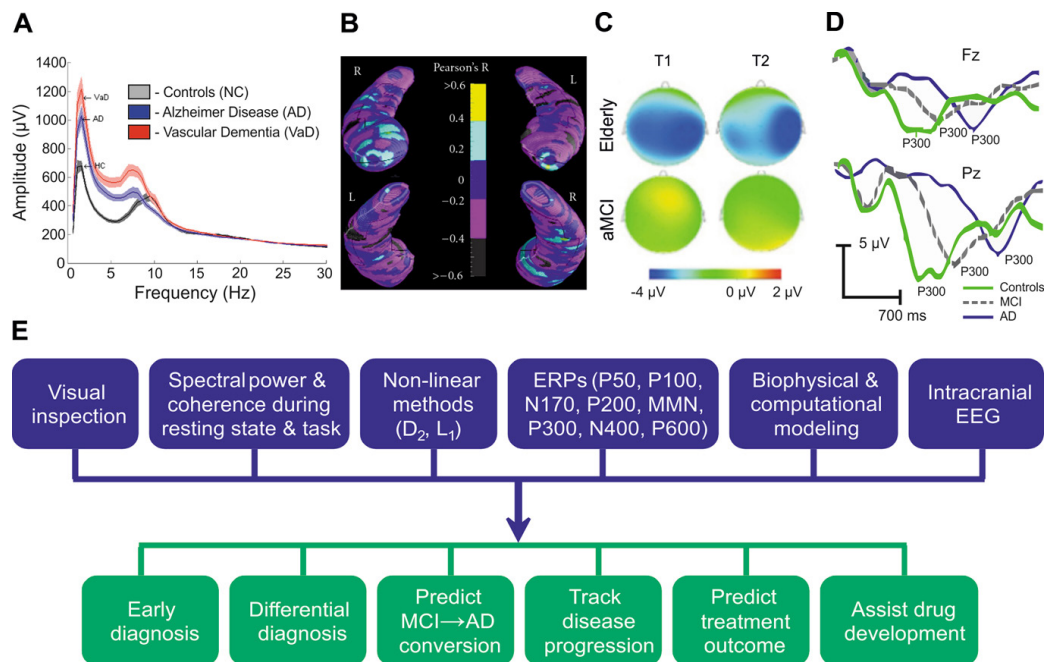


Figure 2. Examples of promising EEG/ERP findings in AD research and a chart summary of potentially useful methods and markers. A) EEG spectral power discriminates between Alzheimer's and vascular dementia. Mean frequency spectrum over the scalp for each group with absolute frequency. Modified with Creative Commons Attribution License from: ref. 272 B) Spectral EEG changes are associated with hippocampus atrophy in MCI and AD. Maps show correlation between alpha3/alpha2 frequency band power ratio and volumes of hippocampal subregions in AD patients. Modified with Creative Commons Attribution License from: ref. 46 C) Decreased auditory MMN in aMCI compared to healthy elderly in a longitudinal study at t1 and t2. Scalp maps show topographical distribution of auditory MMN responses in elderly and aMCI. Modified with Creative Commons Attribution License from: ref. 240 D) Patients with MCI and AD show delayed P300 latencies and attenuated P300 amplitudes compared to controls. Modified with Creative Commons Attribution License from: ref. 172 E) A summary of existing and emerging methods as well as the main EEG/ERP candidate markers that have been used in dementia research. The flowchart highlights the main areas of potential clinical applications of EEG/ERP-derived biomarkers.

The further development of both experimental and clinical neurophysiological methods is important and may have the following directions:

5.1. Experimental and analysis methods

Rapid translation of promising experimental methods to clinical application is essential. To facilitate that it is necessary to increase the dialogue between basic science and clinical research.

The development and translation of different state-of-art research methods may allow near-experimental investigations also in clinical settings, like invasive EEG recordings for diagnosing hidden epileptic activity or to date unknown EEG phenomena.

Modern biophysical modeling tools, such as DCMs, allow us to infer hidden parameters of the network dynamics underlying the observed EEG/ERP signals, and they might allow quantification of the status of neurotransmitter systems in specific circuits. To improve replicability of findings in the field we suggest that future studies should apply preliminary power analysis and include samples of sufficient size. Furthermore, we emphasize the proper use of EEG/ERP processing and statistical analysis methods.

5.2. Clinical studies

Quantitative methods should be routinely used in the clinical practice of diagnosis and/or differential diagnosis of dementias. For this, normative databases need to be generated and standardized evaluation criteria should be developed. As part of this initiative statistical methods for population-based analyses (e.g., z-score analysis) should be introduced and disseminated. Furthermore, we recommend communicating the effect size in future studies in addition to statistical significance as it can provide information about the practical importance of the findings and allow systematic comparisons (meta-analyses).

To enhance the sensitivity and specificity of these methods a promising further step might be the combination of various neurophysiological tools. Developing combined systems of clinical neurophysiology with automatized spectral power, coherence, sleep and non-linear analyzing software products, could allow examining different parameters by one single device. This might be useful in quantifying the concordance of different neurophysiological abnormalities which, in turn, might increase diagnostic efficiency. The alteration of a single neurophysiological

parameter is insufficient for a diagnosis of any type of dementia, however if different types of deviations point to the same direction, the diagnostic accuracy might increase.

To better understand the progressive nature of neurodegenerative diseases it is important to perform serial longitudinal neurophysiological investigations together with neuropsychological testing of healthy subjects, starting in their symptom-free youth, to identify relationships between neurophysiological changes and cognitive decline.

An important aspect of any future direction is making the information available for the scientific community, for avoiding the reproduction of research data and to facilitate progress. The recent revolution in cloud-based internet applications has provided us with easy-to-use and safe tools to exchange information. We encourage data sharing in public databases and dissemination of results in open access format should facilitate the data sharing between the physicians and researchers and distribute the current results more efficiently with preferring the open access publication methods.

The involvement of descriptive and/or quantitative neurophysiological methods in the diagnostic protocols of various dementias has utmost importance and should be strongly encouraged.

6. ACKNOWLEDGEMENT

Our research was supported by the National Brain Research Program (KTIA_NAP_13-1-2013-0001) and MET Hungary Ltd. There are no conflicts to disclose.

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Key Words: Alzheimer's disease, Mild Cognitive Impairment, Electroencephalography, Sleep, Event-Related Potentials, Mismatch Negativity, Review

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