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TREATMENT EFFECTS ON EVENT-RELATED EEG POTENTIALS AND OSCILLATIONS IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease dementia (ADD) is the most diffuse neurodegenerative disorder belonging to mild cognitive impairment (MCI) and dementia in old persons. This disease is provoked by an abnormal accumulation of amyloid-beta and tauopathy proteins in the brain. Very recently, the first disease-modifying drug has been licensed with reserve (i.e., Aducanumab). Therefore, there is a need to identify and use biomarkers probing the neurophysiological underpinnings of human cognitive functions to test the clinical efficacy of that drug. In this regard, event-related electroencephalographic potentials (ERPs) and oscillations (EROs) are promising candidates. Here, an Expert Panel from the Electrophysiology Professional Interest Area of the Alzheimer's Association and Global Brain Consortium reviewed the field literature on the effects of the most used symptomatic drug against ADD (i.e., Acetylcholinesterase inhibitors) on ERPs and EROs in ADD patients with MCI and dementia at the group level. The most convincing results were found in ADD patients. In those patients, Acetylcholinesterase inhibitors partially normalized ERP P300 peak latency and amplitude in oddball paradigms using visual stimuli. In these same paradigms, those drugs partially normalize ERO phase-locking at the theta band (4-7 Hz) and spectral coherence between electrode pairs at the gamma (around 40 Hz) band. These results are of great interest and may motivate multicentric, double-blind, randomized, and placebo-controlled clinical trials in MCI and ADD patients for final cross-validation.

ABBREVIATIONS

Aβ42	Amyloid-beta 42 peptide
ACh	Acetylcholine
AChEIs	Acetylcholinesterase inhibitors
ADD	Alzheimer's disease dementia
ASSR	Auditory steady-state responses
CSF	Cerebrospinal fluid
EEG	Electroencephalography
ERPs	Event-related potentials
EROs	Event-related oscillations
fMRI	Functional magnetic resonance imaging
FDG-PET	Fluorodeoxyglucose positron emission tomography

MCI	Mild cognitive impairment
MEG	Magnetoencephalography
ADMCI	Mild cognitive impairment due to Alzheimer's disease
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
p-tau	Phospho-tau protein

Keywords

EEG, ERPs, EROs, oscillations, P300, event-related, dementia, Alzheimer, biomarker, treatment, monitoring, mild cognitive impairment

1. INTRODUCTION

Increased expectancy of life leads to the growth of the aged population and the increase of cases of dementia, defined as severe cognitive deficits associated with loss of autonomy and disabilities in the activities of daily living. Around 50 million people suffer from dementia worldwide, and its cost reaches up to a trillion US dollars annually (WHO Guidelines, 2019; Alzheimer's Association, 2021).

Alzheimer's disease dementia (ADD) is a progressive neurodegenerative disease that represents the most common cause of age-related dementing illnesses (World Alzheimer Report, 2020). Its pathological changes start as an abnormal accumulation of amyloid-β and tau proteins in the brain several years earlier than the first objective clinical manifestations (Insel et al., 2021). Along the continuum of the clinical manifestations of ADD over time, mild cognitive impairment with preserved autonomy in the activities of daily living is considered a frequent clinical milestone among the clinical predementia stages (Albert et al., 2011).

Scientific advance on AD has been revolutionized by biomarkers that have transformed treatment practices. Various biomarkers for indicating neurodegeneration and pathologies related to abnormal deposited peptides, namely amyloid-beta or tau, have been suggested as objective measures to reflect underlying pathophysiology (Jack et al., 2016; Ehrenberg et al., 2020; Jack et al., 2018; Dubois et al., 2016).

Abnormal deposited peptides such as amyloid-beta and tau define the presence of insidiously developing dementia with core symptoms of episodic memory and/or impairment of other cognitive domains along with biomarkers with a classification so-called AT(N), derived from acronyms of two deposited peptides, Amyloid-beta and Tau, and Neurodegeneration (Jack et al., 2018). Amyloid-beta and tau peptides can be detected by ligand-based positron emission tomography techniques (Janelidze et al., 2017; La Joie et al., 2020) or by a lumbar puncture to detect their levels in the cerebrospinal fluid (CSF) (Blennow and Zetterberg, 2018). Neurodegeneration can be demonstrated by brain atrophy in structural magnetic resonance imaging (Barthélemy et al., 2020) or a low level of glucose uptake indicated by FDG-positron emission tomography (Leuzy et al., 2019). The usefulness of these valid biomarkers in routine clinical use is still arguable, not only because of their invasiveness and cost but also because of their limited specificity and sensitivity rates (Isaacs and Boenink, 2020). Very recently, plasma-

based fluid markers have entered the scene, so now, amyloid-beta, p-tau, and NfL can be measured reliably in both CSF and blood (Ashton et al., 2021). Plasma-based measures of P-tau, either phospho-tau217 (Palmqvist et al., 2020) or phospho-tau181 (Janelidze et al., 2020), show promise reflecting levels of the pathological precipitations in the CSF or brain. They have been announced to provide diagnosis rates of 85% and 98%, respectively, and cross-validated by PET, genetic status, or CSF studies (Mielke et al., 2018; Leuzy et al., 2020; Karikari et al., 2020; Palmqvist et al. 2020). Currently, the use of the latest plasma biomarkers awaits confirmation in larger trials and their incorporation into guidelines, and all the above-mentioned methods relating to pathological features of ADD cannot be applied widely in clinical settings.

Unfortunately, there are no treatment options able to cure the disease. Concerning the licensed symptomatic treatments for ADD, cholinesterase inhibitors, memantine, and a combination of a cholinesterase inhibitor and memantine have produced statistically significant but clinically small delays in various domains of cognitive and functional decline in patients with AD and MCI due to AD (Dubois et al., 2015; Schmidt et al., 2015; Matsunaga et al., 2019; Ismail et al., 2020).

In June 2021, the Food and Drug Administration (FDA) suggested Aduhelm (aducanumab) for the treatment of ADD as the first disease-modifying drug (Knopman et al., 2019). However, the European Medicines Agency has recommended the refusal of a marketing authorization for Aduhelm due to concerns about safety and efficacy (Mahase, 2021). Therefore, there is an urgent need to identify and use biomarkers probing the neurophysiological underpinnings of human cognitive functions to test the clinical efficacy of that drug at the group level. In this regard, event-related electroencephalographic potentials (ERPs) and oscillations (EROs) are promising candidates, which are available worldwide, including in lower and middle-income countries (Babiloni et al., 2020a; Babiloni et al., 2020b; Rossini et al., 2020). It is widely used as a non-invasive, user-friendly, and low-cost technique, and it can also be implemented on almost any computer system.

Notably, the Steering Committee of the Electrophysiology Professional Interest Area (EPIA) of The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART; https://www.alz.org/) appointed expert panels for reviewing the scientific literature on ERP and ERO biomarkers in patients with ADD and related disorders to

test the hypothesis that those biomarkers may reflect the effects of ADD on cerebral cognitive systems. The outcome has been recently published (Babiloni et al., 2021; Güntekin et al., 2021) and is summarized in the following paragraphs.

1.1. Event-Related Potentials (ERPs)

Event-related EEG measures during oddball tasks may be helpful cognitive neurophysiological biomarkers for intervention clinical trials performed in individuals with AD (Güntekin et al., 2021). Previous studies confirm that validated neuroimaging and multimodal fluid AD biomarkers are significantly associated with event-related EEG responses during oddball tasks (Babiloni et al., 2020, Babiloni et al., 2020b, 2021). It is well known that ERPs allow for the study of EEG activity phase-locked to sensory stimuli or motor responses during cognitive tasks. Those potentials are typically computed by averaging artifact-free EEG activity recorded during sensory stimuli using the onset of the stimulus or motor response as a zero time. The most popular ERP paradigm used in MCI and ADD patients is the so-called "active oddball task" (Donchin et al., 1973; Polich and Kok, 1995; O'Connell et al., 2012; Quiroz et al., 2011; Jiang et al., 2021) in which frequent (70-80%) and rare (30-20%) auditory or visual stimuli are delivered, and experimental subjects must respond to the rare stimuli by pressing a button or counting the stimuli.

A negative deflection, which is called the N100 component, is observed when an unexpected stimulus is presented. It is involved with the primary perceptual processing of incoming information and early attentional allocation to visual stimuli (Lijffijt et al., 2009). P100 is a positive wave elicited by different types of visual stimuli only and is related to early visual processing (Heinze and Mangun, 1994). The recognition of facial expressions (Bentin et al., 1996; Başar et al., 2006, 2007; Güntekin and Başar, 2007; Puce et al.,2013; Güntekin et al., 2017, 2019; Fide et al., 2019; Güntekin and Başar, 2014) or ambiguous figures (Başar-Eroğlu et al., 1996; Mathes et al., 2006; Strüber et al., 2000; İşoğlu-Alkaç et al., 2000) are among the most complex functions in the visual cognitive processes. Previous studies in MCI and ADD patients showed mixed findings in P100 and N100 components, possibly due to their sensitivity to multiple information processes and disease status (Lijffijt et al., 2009). As compared to CU persons, MCI patients showed increased P100 amplitude for visual stimuli with familiar vs unfamiliar faces (Saavedra et al., 2012), while ADD patients had no difference in the P100

following familial vs. unfamiliar faces and scenes (Cheng and Pai, 2010). Other studies showed inconsistent results in ADD patients as increased P100 amplitude and latency in the recognition of emotional face expressions (Fide et al., 2019), or decreased P100 latency in a visual attentional task with low sensitivity (50% of the group) (Fernandez et al., 2007), or unchanged visual P100 and N100 latencies during facial discrimination and active auditory oddball demands (Kurita et al., 2010). Similar variability of the results was reported for N100. MCI patients showed decreased N100 amplitude during a task asking "congruous/incongruous" statements on visual stimulus pairs (Olichney et al., 2006) whilst no difference in P100 or N100 amplitude or latency between CU and MCI or ADD patients was observed in an active auditory oddball task at baseline and 1-year follow-up (Lai et al., 2010) as well as in visual tasks requiring detection of stimulus motion (Yamasaki et al., 2012), semantic priming of word pairs (Grieder et al., 2013), and working memory as 2-back or matching-to-sample demands (Deiber et al., 2015).

The N200 component of ERPs typically peaks in amplitude during cognitive demands, especially active oddball tasks. It reflects selective attention and perceptual (stimulus discrimination) processes (Patel and Azzam, 2005; Pennys et al., 2007). In the oddball paradigm, N200 can be divided into N200a (i.e., mismatch negativity, MMN) and N200b components. N200a (MMN) and N200b are negative going ERP components that reflect preattentive (automatic) and conscious brain responses to deviant stimuli during oddball tasks, respectively (Näätänen et al., 1978, 2005). In this paper we did not include the event-related responses elicited after passive tasks, therefore the N200b will be mentioned as N200 from now on. Using an active auditory oddball task, the N200 latency reliably predicted the progression from MCI to ADD status in relation to CSF amyloid-β levels (Papaliagkas et al., 2009), while the N200 amplitude was progressively smaller at the follow-ups of about 1 and 2 years (Papaliagkas et al., 2011). In a recent review paper, 22% of reviewed studies between MCI and CU groups reported a significant difference in N200 amplitude, whilst the rate was 18% between ADD and CU groups (Paitel et al., 2021). More specifically, some studies reported smaller N200 amplitude in both MCI and ADD groups over the CU groups (Fernandez et al., 2013; Wang et al., 2013; Bagattini et al., 2017), while some others stated no difference in N200 between MCI and CU groups (Cespón et al., 2015a; Mudar et al., 2016) or between CU and ADD groups (Bagattini et al., 2017). The above-mixed results might be due to the different variants of the oddball tasks used as the kind of stimuli, the inter-stimulus intervals, the task duration, the level of required attention to the stimuli and experimental conditions, and the kind of subject's responses required

during ERP recordings (Morrison et al., 2019). Other sources of variability are the procedures for the enrollment of patients and diagnosis of ADD and clinical severity of the disease. In most of the studies, the diagnosis of ADD did not use in-vivo measures of abnormal levels of amyloid-beta and tau in patients' brains. In those studies, MCI patients showed different domains of cognitive functions affected, namely significant factors influencing N200 in MCI patients (Cespón et al., 2013, 2015a, b).

The P200 response constitutes another component of the ERPs. It is associated with early attentional allocation to visual stimuli and is involved with the primary perceptual processing of incoming information (Omoto et al., 2010). Earlier studies in MCI and ADD patients showed mixed findings as well. Zunini et al. (2016) compared individuals with MCI and CU persons via an n-back working memory task with baseline (0-back), low load (1-back), and high load (2-back) working memory conditions revealing delayed P200 latencies in MCI relative to control participants in all conditions Similarly, Missonnier et al. (2007) reported that progressive MCI and ADD groups had longer P200 latencies than stable MCI and CU persons during the 2-back task at one-year follow-up. In ADD patients, visual P200 amplitude was also found to be decreased during visual tasks requiring detection of stimulus motion (Yamasaki et al., 2012a). On the other hand, two studies are reporting contrary findings. P200 latencies did not differ between CU persons and patients with ADD during facial discrimination and active auditory oddball tasks (Kurita et al., 2010), and between CU individuals and MCI patients during medium-term memory retrieval of faces with emotional expressions (Schefter et al., 2013).

ERPs following the target stimuli show a parietal ample positivity (P) reflecting focused attention, decision making, and working memory (Donchin et al., 1973, Polich and Kok, 1995; O'Connell et al., 2012). The P300 is one of the most studied ERP components investigating cognitive functions. P3a and P3b constitute the subcomponents of P300. P3a is generated when stimuli are processed if sufficient attentional focus is engaged. P3b occurs when subsequent attentional resource activations promote memory functions in temporal-parietal areas (Polich, 2007). In this paper we did not include the P300 responses elicited after passive tasks, therefore the P300b will be mentioned as P300 from now on. In the literature, reduced P300 amplitudes and longer P300 latency of memory target-related ERPs in an active oddball task were reported in MCI and ADD patients compared with cognitively unimpaired (CU) subjects. Sufficient evidence exists to suggest that the amplitude and latency of the P300 change in AD (Polich,

1989; Pokryszko-Dragan et al., 2003; Katada et al., 2004; Polich and Corey-Bloom, 2005; Ally et al., 2006; Muscoso et al., 2006; Caravaglios et al., 2008; Bonanni et al., 2010; Lai et al., 2010; Pedroso et al, 2012; Babiloni et al., 2020). Furthermore, characteristics of the P300 are also altered in individuals with MCI (Frodl et al., 2002; Golob et al., 2002; Bennys et al., 2007; van Deursen et al., 2008; Lai et al., 2010; Parra et al, 2012; Cid-Fernandez et al., 2019; Babiloni et al., 2020). Other studies suggest that features of the P300 wave might provide evidence for the conversion of MCI into AD (Golob et al., 2002, 2009; Papaliagkas et al., 2008; van Deursen et al., 2008; Babiloni et al., 2020). Although prolongation of latency occurs as a function of time in physiological aging (Papaliagkas et al., 2011a), the P300 wave has been demonstrated to be sensitive to ADD neuropathology (Morgan and Murphy, 2002; Papaliagkas et al., 2009; Fernandez et al., 2007) as either P300 latencies correlate with Ab42 levels in MCI patients, or with baseline levels in a longitudinal study (Papaliagkas et al., 2009, 2011b), or in genetically PSEN mutation carriers that lead to familial AD, altered P300 parameters have been identified 10 years before the disease onset (Golob et al., 2009; Quiroz et al., 2011). Taken together these results suggest that the P300 could contribute to the assessment of AD.

There were also alterations in patients with ADD and CU individuals regarding ERP components after linguistic semantic stimuli and repeated words. CU persons had larger N400 amplitude over parietotemporal regions in response to semantically incongruous stimuli (Kutas and Federmeier, 2011). Linking this effect to semantic memory, semantic incongruity caused reduced responses in physiological aging, and they were further reduced or abolished in N400 in ADD (Olichney et al., 2006). The late positive component (LPC or P600) is elicited during the memory encoding and retrieval processes of words. In CU subjects, P600 displays a significant word repetition effect as attenuation of their amplitude, while the attenuation of the N400 or P600 after repeated words was lower in MCI and predictive of ADD development (Olichney et al., 2002a, Olichney et al., 2006). The ERP components, their functions, and possible generators are summarized in Table 1.

1.2. Event-Related Oscillations (EROs)

The ongoing EEG activity recorded during cognitive tasks can also be analyzed linearly to explore event-related alterations in power or phase characteristics related to the ongoing oscillatory responses or the event-related synchronization/desynchronization (ERS/ERD) at delta, theta, alpha, beta, and gamma frequency bands (Lopes da Silva, 1990). Cognitive ERPs

can be decomposed to unveil the phase-locked EEG delta, theta, alpha, beta, and gamma oscillations named EROs (Başar-Eroğlu & Başar, 1991; Herrmann and Knight, 2001; Lejko et al., 2020). EROs that were elicited after digital filtering or other transformation methods were repeatedly investigated in oddball tasks. Previous EEG studies from independent research teams have consistently demonstrated reduced EROs at delta and theta frequencies in MCI and ADD patients over CU seniors during oddball tasks (Karrasch et al., 2006; Güntekin et al., 2008, 2019; Cummins et al., 2008; Yener et al., 2008, 2012; Caravaglios et al., 2008; Başar et al., 2010; Michalopoulos et al., 2012; Deiber et al., 2015; Tülay et al., 2020). Patients with MCI had lower theta and beta EROs than individuals with stable MCI (Hedges et al., 2016, Jiang et al., 2015, Missonnier et al., 2007). More detailed information on event-related oscillations can be found in the fourth section.

The pioneering work on oscillatory dynamics in animals was reported by Freeman (1975), Başar et al. (1975a, 1975b, 1975c), and Başar (1980), showing the distributed oscillatory responses in all parts of the brain. According to Başar et al. (2001), event-related potentials constitute the superposition of oscillations in certain frequency bands by applying time-frequency (TF) analyses to ERPs activity (Başar-Eroğlu et al., 1992, 2001; Başar et al., 2001; Demiralp et al., 2001; Karakaş et al., 2000; Yordanova et al., 2002; Makeig et al., 2002; Gilmore et al., 2010).

Although the averaged ERPs are useful and commonly used methods, their further computation yields information about the brain's intrinsic activity and dynamic changes even more. As mentioned previously, the brain oscillatory activities after an “event” display almost inverse dynamics to those during the resting condition (Başar, 1980; Başar-Eroğlu et al., 1991; Babiloni et al., 2020). In the case of evoked potentials elicited by an “event” or stimuli are enhanced in amplitude when preceded by low-amplitude pre-stimulus alpha or theta rhythms (Başar et al., 1984; Jasiukaitis and Hakerem, 1988; Başar-Eroğlu et al., 1992; Babiloni et al., 2008). In these studies, delta and theta EROs responsiveness in frontal lobes was interpreted as an indication of the well-functioning of the hippocampo–fronto–parietal system during cognitive processes. For this reason, the role of oscillatory activities in certain frequency bands will be listed and explained below.

1.2.1. Delta frequency band (<4 Hz)

The shape of the P300 complex is formed basically by the superimposition of delta response oscillating at 2 Hz (Başar-Eroğlu, Başar, 1991; Başar-Eroğlu et al., 1992; Schürmann et al., 2001), along with prolonged theta and alpha oscillatory responses (Kolev et al., 1997), but activity changes in faster frequency bands also contribute (Karakaş et al., 2000; Sakowitz et al., 2001; Spencer and Polich, 1999). A study of 2068 participants (Bernat et al., 2007) confirmed that the major operating rhythms of the P300 were delta and theta oscillations. Not only the oddball paradigm but also others including error-related negativity, feedback negativity, N2/P3 of go/no-go tasks involved delta and theta oscillatory responses (Bernat et al., 2012; Harper et al., 2014; Schmiedt-Fehr and Başar-Eroğlu et al., 2011).

Long-lasting depolarization of cortical pyramidal cells produces delta oscillations (Steriade and McCarley, 1990). Other than this, thalamocortical cells (Steriade et al., 1993), neuronal cells in the nucleus accumbens (Leung and Yim, 1993), in the ventral tegmental area, in the ventral pallidum (Lavin and Grace, 1996), and glial cells also yield delta rhythms (Amzica and Steriade, 2000). The delta EROs were elicited as a negative peak at +200 ms post-stimulus and continued with a positive peak around +400-600 ms post-stimulus. During this wave, superimposed theta responses either enhance or dampen the signal, whilst alpha prolongation implies the achievement of a cognitive goal (Güntekin and Başar, 2016). The prestimulus delta state affects the post-stimulus responses as an inverse relation between them, as suggested for the first time by Başar et al. (1984) and Başar and Stampfer (1985) as they reported when a stimulus was applied in certain interstimulus intervals, a phase reordering occurred in delta and alpha bands after the stimulus. Regarding the task's difficulty, stimulus with greater cognitive load elicited larger P300 and single-trial delta response amplitude (Mathes et al., 2012). Delta EROs (Başar and Stampfer, 1985; Stampfer and Başar, 1985) behave as a general electrophysiological marker in cognition (Güntekin and Başar, 2016), and they are involved in cognitive processes related to decision making and attention processes (Knyazev, 2012). Regarding connectivity, delta synchronization is observed between frontocentral and parietal (Qassim et al., 2013) regions during attention and memory updating in a MEG (Ishii et al., 2009) and EEG study (Güntekin and Başar, 2010). In various studies, an unspecified decrease of delta ERO power decrement is encountered in ADD, MCI, schizophrenia, Parkinson's disease (PD), or bipolar disorder (Başar et al., 2013). In ADD, an increment in rsEEG delta band power is reported,

suggesting a similarity to those in the prestimulus era (Babiloni et al., 2015, 2018a, 2018b, 2019a; Jelic et al., 2000; Caravaglios et al., 2008) and a diminished delta EROs after an event (Caravaglios et al., 2008; Yener et al., 2008, 2012), supposing an increased delta response would not be produced in such a busy network (Rahn and Başar, 1993). A delay in peak delta EROs and a gradual decrease in the amplitude of delta EROs in the aging of CU individuals (Emek-Savaş et al., 2016), or across the AD spectrum have been noted (Başar et al., 2016b). Frontal delta EROs (visual and auditory) have been attenuated in MCI (Kurt et al., 2014; Yener et al., 2013) or ADD patients compared with CU persons (Yener et al., 2009, 2012). EROs were also sensitive to ADD progression over time (Yener and Başar, 2013). However, the delta or theta EROs power decrease cannot be considered as specific to ADD, as patients with Parkinson's disease dementia (PDD) (Güntekin et al., 2019) or PD-MCI also display lower ERP amplitudes/delta or theta EROs measurements (Yener et al., 2019; Güntekin et al., 2018, 2020; Hünerli et al., 2019).

1.2.2. Theta frequency band (4-7 Hz)

During elicitation of an ERP response, oscillatory responses in theta ranges (4-7 Hz) form the early components of the P300 complex and later parts by delta response (Başar-Eroğlu et al.,1992; Kolev et al., 1997; Karakaş et al., 2000). The relation between theta oscillatory activity and working memory under physiological conditions has been implicated by many studies (Klimesch et al., 1997; Jensen and Tesche, 2002; Pavlov and Kotchoubey, 2017; Zakrzewska and Brzezicka, 2014; Borhani et al., 2021), and in ADD (Klimesch et al., 2005). Experimental studies indicate that synchrony in the theta oscillatory activity represents one of the most studied neuronal activities in the mammalian hippocampus, and it is associated with the top-down control of cognitive processes (Vertes, 2005). The hippocampal formation and the medial septum generate theta oscillations, and they act as a pacemaker for generating theta oscillatory rhythm in prefrontal cortical networks (Thierry et al., 2000). This strong connection generated by theta rhythm synchronizes medial prefrontal cortex neurons to spatially distributed cortical areas, consequently strengthening synaptic links, and facilitates the transfer of hippocampal information to the neocortex during learning and memory (Ahnaou et al., 2014; Buzsaki, 2002; Paz et al., 2008). During active cognitive or motor tasks, enhanced EEG theta coherence has been observed between the hippocampus, prefrontal, and posterior association cortices (Womelsdorf and Fries, 2006; Seemüller et al., 2012; Schmidt et al., 2013).

In experimental studies, it has been shown that oscillations from each frequency band are considered to subserve a different function and to have a different underlying mechanism. Synchronous oscillatory rhythms in the slow theta frequencies (i.e. theta coupling) represent the main mechanism for coordinating disparate brain networks temporally during cognitive tasks, including attention and working memory (Lisman and Buzsaki, 2008; Singer, 1999; Ahnaou et al., 2014). Several studies with a focus on the generators of theta rhythm indicated specific hippocampal and other brain regions (Buzsáki and Watson, 2012). Theta oscillatory activity is considered to coordinate the information flow and establish temporal regulations to propagate across selectively distributed neuronal networks in the entorhinal cortex and the subregions of the hippocampus (Cappaert et al., 2009).

Event-related spectral perturbation evaluates the dynamic alterations in power at frequency ranges as a function of time relative to a pre-stimulus baseline (Makeig, 1993), while it also allows measuring increases and decreases in power spectrum with the use of event-related synchronization (ERS) and desynchronization (ERD). A decrease in the early induced theta ERS indicates a rapid cognitive decline among the individuals with MCI, and similar values of theta ERS to that of the HC group may imply a stable MCI. Even though MCI patients were successful in achieving the behavioral tests, the frontal theta (in the range of 4-6 Hz) EROs discriminated progressive MCI from both the stable MCI and the HC group and were suggested as an early electrophysiological marker of cognitive decline (Hedges et al., 2016; Jiang et al., 2015; Missonnier et al., 2007; Deiber et al., 2009). This finding can be explained based on the recruitment of additional cortical networks that make the individuals achieve the behavioral tasks and maintain a high-performance level, with an impaired prefrontal activity detected by electrophysiology.

Theta ERD responses are found higher in the MCI group than ADD group (Fraga et al., 2018), and the theta EROs power is decreased in both MCI and more profoundly in PD-MCI groups (Yener et al., 2019), in addition to phase-locking impairment in the theta band. MCI patients display reduced levels in both total delta (Tülay et al., 2020) and theta EROs power (Deiber et al., 2009; Nguyen et al., 2017; Tülay et al., 2020) in the early courses of disease, whereas reduction of evoked delta power starts in the MCI stage but becomes distinctive later in the phase of dementia of ADD (Caravaglios et al., 2010; Tülay et al., 2020). The distinctive pattern of total and evoked the power of slow waves in the temporal evolution of ADD may

reflect the neurodegenerative spreading pattern that involves subcortical limbic and association cortices at the beginning and later involvement of lower-level cortical areas or thalamocortical circuits. Also, theta connectivity is prominently affected in ADD (Yener and Başar 2013; Güntekin et al., 2008), and theta gamma coupling showed a gradual decrease along with the HC, MCI, and ADD (Goodman et al., 2018). Similar to delta band activity, theta EROs are not specifically reduced in ADD, but in other cognitive impairments such as PD (Yener et al., 2019; Güntekin et al., 2018, 2019, 2020).

1.2.3. Alpha frequency band (8-12 Hz)

Alpha EROs in ADD patients display a more complex picture than other slow-wave EEG-EROs responses. They have been shown to relate to memory-related cognitive processes (Klimesch et al., 1997, 2006, 2007; Maltseva et al., 2000, Doppelmayr et al., 2005; Sauseng et al., 2005; Wang et al., 2017). However, there are controversies on the direction of alpha responses and memory processes. Some researchers found alpha ERD responses during semantic memory processes as a functional correlate of brain activation (Klimesch et al., 1997, 2007). On the other hand, some other groups demonstrated increased cognitive function and attentional processes about the increased alpha responses (Jensen et al., 2002; Palva and Palva, 2007; Tuladhar et al., 2007; Scheeringa et al., 2009), and some reported post-stimulus event-related alpha synchronization in relatiabout duality at the time point of stimulus onset" including the amplitude of or phase-angle of the pre-stimulus alpha activity (Başar, 2012; Başar and Güntekin, 2012). The variety of findings on alpha EROs responses may be based on their having multiple roles in sensory, cognitive, emotional, and motor-related processes; and the inverse relationship between pre-stimulus EEG and post-stimulus alpha power may influence the consequent behavioral performance (Ergenoğlu et al., 2004; Busch et al., 2009; Babiloni et al., 2000, 2008; Samaha and Postle, 2015).

In line with these views under physiological conditions, several ERD/ERS studies reported contradictory results spanning from post-stimulus alpha ERD decreases in ADD and MCI patients (Fraga et al., 2017), to finding decreased alpha ERS in ADD (Babiloni et al., 2000) and MCI (Karrasch et al., 2006); or decreased ERD over the anterior regions during the pre-event era, while an increased ERS over the posterior regions during the post-stimulus era in MCI patients (Caravaglios et al., 2015). A further study on the multidomain MCI group had a more

profound alpha ERS decrease than single domain MCI (Deiber et al., 2010). Also, power or phase-locking measurements of alpha EROs were diminished (Deiber et al., 2010) in progressive MCI compared to CU individuals (Michalopoulos et al., 2012). In several intra-hemispheric alpha EROs coherence studies indicating brain functional connectivity, ADD patients showed decreased memory-related connectivity (Başar et al., 2010; Hogan et al., 2003). On the other hand, the inter-hemispheric EEG coherence was higher in MCI patients when memory demand increased (Zheng et al., 2007). A compensating rsEEG hyperconnectivity in the early stages of ADD has been emphasized in recent studies (Bonanni et al., 2021). Yet, other explanations can be made for these contradictory findings. Prodromal ADD patients show abnormal thalamocortical interactions, possibly due to impairment of the cortical gray matter, especially in posterior regions (Babiloni et al., 2014). This abnormality of wakefulness cortical alpha sources can be based on a progressive alteration in the interplay of thalamocortical high threshold GABA-ergic interneurons, thalamocortical relay-mode, and cortical pyramidal neurons (Hughes and Crunelli, 2007; Crunelli and Hughes, 2010). During wakefulness, under physiological conditions, glutamatergic and cholinergic signaling to this complex network augments the generation of cortical and thalamocortical alpha rhythms, resulting in cycles of excitation and inhibition within a time frame of approximately 70-100 milliseconds (Hughes and Crunelli, 2007; Crunelli and Hughes, 2010, Jovicich et al., 2019). In order to understand these complicated responses in alpha frequency ranges, further studies are needed to explore the dynamic alpha changes during the task in ADD patients, especially taking both prestimulus era, and post-stimulus era alpha changes into consideration.

1.2.4. Beta frequency band (13-30 Hz)

The increased beta responses have been reported as related to attention, emotion recognition, primary sensory processing, and movement (Engel and Fries, 2010). In CU persons, increased ERO power or phase-locking of beta responses upon presentation of target stimuli in healthy subjects imply that beta EROs oscillations could shift the system to an attention state which serves as one of the bases of cognitive functions (Wróbel et al., 2000; Güntekin and Başar 2007). Another role of beta responses was reported in emotional processes, especially during the perception of negative emotional stimuli (Miskovic and Schmidt, 2010; Woodruff et al., 2011; Güntekin and Başar, 2014). These results placed beta ERO responses among one of the widely used frequency bands in the EEG based emotion recognition algorithms (Zhang et al., 2016;

Mohammadi et al., 2017; Munoz et al., 2018) and in movement-related cognitive functions; (Cacace and McFarland, 2003; Mazaheri and Picton, 2005; Ishii et al., 2009), or in cognitive paradigms (Tallon-Baudry et al., 1998; Peterson and Thaut, 2002; Onton et al., 2005; Ravizza et al., 2005; Güntekin et al., 2013). In a review article, Engel and Fries (2010) discussed that beta EROs may occur because of sensory processes, such as increased beta responses were elicited over the occipital cortex by visual stimuli (Senkowski et al., 2006) and over central and temporal locations by auditory stimulation (Haenschel et al., 2000; Sakowitz et al., 2005; Senkowski et al., 2006). Also, multisensory stimuli enhanced higher beta responses than single sensory stimuli (Sakowitz et al., 2005; Senkowski et al., 2006). In the pathological conditions, MCI patients show lower beta EROs (Güntekin et al., 2014; Caravaglios et al., 2018), with a gradual decrease in progressive MCI patients in comparison to stable MCI patients (Hedges et al., 2016; Jiang et al., 2015; Missonnier et al., 2007).

1.2.5. Gamma Frequency Band (30-45 Hz)

The significance of the evoked gamma-band activity, especially 40 Hz, has been emphasized in the central nervous system of a variety of animals including snails, vertebrates, and humans, as an important element in processing sensory and cognitive information in neural networks (Freeman, 1975; Başar et al., 1987; Başar-Eroğlu and Başar, 1991; Eckhorn et al., 1988; Gray and Singer, 1987; Lenz et al., 2008; Traikapi and Konstantinou, 2021). Gamma frequency band is more likely to relate to attention, or attentional selection (Fries et al., 2001; Bichot et al., 2005; Womelsdorf and Fries, 2006, 2007) as heightened connectivity at gamma frequencies (30 –100 Hz) has been elicited during states of cue detection (Howe et al., 2017). The relationship between memory and gamma responses has been shown in many reports (Başar, 2013; Başar-Eroğlu et al. 1996; Herrmann et al., 2004; Jokisch and Jensen, 2007; Singer, 1999; Tallon-Baudry and Bertrand, 1999). Inhibitory GABAergic interneurons have a direct modulatory effect on gamma oscillations (Gray and McCormick, 1996; Herrmann and Demiralp, 2005), and combinations of various transmitters play a role in even the simplest cognitive responses. In previous studies, GABA, GABA/glutamate, and dopamine have been reported as the neurotransmitters that influence the gamma frequency (Whittington et al., 1995; Gray and McCormick, 1996; Muthukumaraswamy et al., 2009; Kömek et al., 2012) which may modulate glutamatergic pyramidal cell activity via inhibitory GABA network (Carlen et al., 2012; Fell et al., 2001; Sederberg et al., 2003; Tallon-Baudry et al., 2005). Gamma oscillatory activity seems

to establish synchronization not only in short-distance local cortical networks (Buzsaki, 2006) but also plays a role in long-range connectivity (Cuesta et al., 2015, Maestú et al., 2008; Jiang et al., 2008).

The abnormalities of gamma connectivity and activity can be seen both during event-related activity in ADD and MCI. Counterintuitively, both the power and connectivity of the EROs gamma-band seem to increase in ADD (Di Lazzaro et al., 2004; Osipova et al., 2006; van Deursen et al., 2011; Ferreri and Rossini, 2013; Başar et al., 2016a; Başar et al., 2017). The uniqueness of gamma frequency band activity in that sense could be explained by an inhibitory interneuron impairment in ADD patients with a subsequent increase in gamma activity (Verret et al., 2012; Palop and Mucke, 2016). Decreased GABAergic inhibition was demonstrated in a mice model of ADD (Busche et al., 2008), and suggested as related to increased gamma responses in ADD patients (Stam et al., 2006; Rossini et al., 2006; Osipova et al., 2006; van Deursen et al., 2008, 2011; Başar et al., 2016a, 2017).

During the cognitive tasks, ADD patients respond with a 25% larger gamma response and a delay about 100 ms later in the higher frequency gamma subband (40-48 Hz) (Başar et al., 2016a) without obvious fluctuations (Başar et al., 2016a; Deiber et al., 2010). Therefore, the gamma EROs display increased power in ADD in contrast to other frequency bands. The delay in cognitive gamma responses in this patient group may be related to lagged connections between cortical, thalamic, and limbic areas because of neurodegeneration during fine-tuning of fast top-down and bottom-up processes related to memory, and other related cognitive functions (Canuet et al., 2015). Furthermore, larger amplitudes in gamma EROs activity may be an index of cortex hyperexcitability that has been reported repeatedly in ADD (Stam et al., 2006; Rossini et al., 2006; Osipova et al., 2006; van Deursen et al., 2008, 2011; Başar et al., 2016a, 2017; Palop and Mucke, 2016).

In the current article, a multidisciplinary panel of experts aimed to review the literature about the effects of medications or interventions on ERO/ERP EEG oscillations during cognitive tasks. As there are two fundamental types of medication for the treatment of ADD, (i.e. AChEI and memantine, a NMDA antagonist), the pharmacological effects of these agents will be emphasized throughout the article.

2. AIMS AND METHODOLOGY

The EPIA Steering Committee formed an expert panel to review the literature and provide recommendations on candidate ERP and ERO measures for characterizing the effects of pharmacological treatments on neurophysiological oscillatory mechanisms in MCI and ADD. The Expert Panel included expert neurologists, psychiatrists, and neurophysiologists from EPIA, Global Brain Consortium (https://globalbrainconsortium.org), and The PDWAVES Consortium (wwwpdwaves.eu). A specific question was addressed: What is the ERP and ERO measure that most consistently reveal the effects of those treatments in ADD patients? To answer, a comprehensive literature search was completed on ERPs and EROs in MCI and ADD.

The literature search was performed on PubMed and Scopus using the keywords given in the below keywords list. Titles and abstracts were searched from these databases. The last search was conducted on February 7, 2021. Duplicated studies were eliminated as a result of two different database searches.

The keywords for the ADD patients were as follows: "Event-Related Potential" AND Treatment AND Alzheimer; "Event-Related Potential" AND Medication AND Alzheimer; P300 AND Medication AND Alzheimer; "Alzheimer's Disease OR Alzheimer" AND "Event-Related Oscillation" AND "Treatment OR Drug OR Medication"; "Alzheimer's Disease OR Alzheimer" AND "Evoked Oscillation" AND "Treatment OR Drug OR Medication"; "Alzheimer's Disease OR Alzheimer" AND "Event-Related Desynchronization OR Event-Related Synchronization" AND "Treatment OR Drug OR Medication."

The keywords for the MCI patients were as follows: "Event-Related Potential" AND Treatment AND Mild Cognitive Impairment; "Event-Related Potential" AND Medication AND Mild Cognitive Impairment; "Mild Cognitive Impairment OR MCI" AND "Event-Related Oscillation" AND "Treatment OR Drug OR Medication"; "Mild Cognitive Impairment OR MCI" AND "Evoked Oscillation" AND "Treatment OR Drug OR Medication"; "Mild Cognitive Impairment OR MCI" AND "Event-Related Desynchronization OR Event-Related Synchronization" AND "Treatment OR Drug OR Medication".

Authors (GY, DHG, and EY) independently reviewed the articles to decide on related articles for inclusion. In case of indecision, the reviewers discussed and decided on the articles in doubt. After careful revision of the searched articles, only related articles were included in the

study. Namely, articles that did not include the treatment-related EEG research on ADD and/or MCI were described as irrelevant articles and not included in the current review. The reference lists of the articles included according to database searches were checked. In the reference lists, if there were studies that did not appear in the database searches but met the related article criteria, they were also included in the study.

The above Authors excluded resting-state EEG studies, EEG-oddball studies using other than active oddball tasks, and studies that did not include the treatment-related EEG research on ADD and/or MCI. Afterward, the mentioned co-Authors produced a first draft of the manuscript circulated to all Panel members. After some rounds of revisions, the Panel reached a unanimous consensus about the findings and recommendations. The manuscript was finalized in December 2021.

The terms and methodological procedures of the reviewed studies do not derive from daily medical practice and were not used for diagnostic, prognostic, or monitoring purposes. Furthermore, the opinions and recommendations of the expert panel do not represent guidelines for the clinical applications to the monitoring of treatments for AD. Indeed, the present methodology did not follow standard procedures typically adopted by international biomedical societies for the review of the medical intervention and practice (e.g., "GRADE", https://gdt.gradepro.org/app/handbook/handbook.html).

In the review of the ERP and ERO studies, we decided to accept those using clinical diagnostic criteria for AD not excluding AD patients with moderate cerebrovascular, non-AD hippocampal impairment (TDP-43), and Lewy body co-pathology. We also used the term MCI to denote patients with MCI even without a diagnosis based on in-vivo biomarkers of AD. It should be also noted that ERP and ERO studies reviewed in the present paper used heterogeneous procedures for the detection of artifacts in preliminary EEG data analysis. The flow chart to summarize the criteria of included and rejected studies for the current paper is demonstrated in Figure 1.

Figure 1. Flow diagram of the literature search. * Exclusion criteria: 1. resting-state EEG studies, 2. EEG-oddball studies using other than active oddball tasks, 3. Studies that did not

include the treatment-related EEG research on ADD and/or MCI, 4. Studies with non-pharmacological interventions (cognitive training, TACS, TMS, TDCS) to assess ERPs/EROs on ADD and/or MCI.

To our knowledge, this is the first international initiative designed to reach consensus recommendations on the optimal ERP and ERO measures to be used in clinical trials testing treatments for ADD patients. We hypothesized that those measures may be sensitive in the detection of the treatment effects at the group level and the outcome may promote the use of them surrogate neural endpoints for monitoring the neurophysiological effects of drugs for ADD on brain cognitive systems. Notably, there are many ongoing phases 2-3 clinical trials targeting amyloid-beta in symptomatic or asymptomatic familial ADD mutation carriers (Cummings et al., 2021). To the best of our knowledge, none of them use ERPs or EROs in monitorization or even in the development of these pharmacological agents to deliver their earliest reflections on neuronal activity. So far, no review has investigated treatment effects on ERPs/EROs observed in MCI/ADD patient groups. In the following section, the pharmacological effects related to each component of ERPs were presented separately.

3. TREATMENT EFFECTS ON EVENT-RELATED POTENTIALS (ERPs)

3.1. The Early Component of ERPs and Treatment Effects

3.1.1. P100, N100, P200

Only five studies were found to investigate treatment effects on the N100 component. The studies on AChEIs did not show any effect on N100. In a small group of ADD, the physostigmine treatment resulted in no alterations in N100 amplitude or latency in an auditory oddball task (Neshige et al., 1988). In the same line, a large group of ADD patients showed no effect of about 2 years of donepezil treatment on N100 amplitude or latency in an auditory oddball task (Chang et al., 2014). Furthermore, nicotine administration did not change P100 and N100 amplitude or latency in auditory and visual oddball tasks between tacrine-treated and non-treated ADD groups (Knott et al., 2002).

Concerning other treatments, a nootropic drug possibly acting on AMPA glutamate and cholinergic receptors (piracetam) mitigated the reduction in N100 latency of auditory and visual

oddball ERPs in ADD patients as compared to CU persons (Dabic-Jeftic and Mikula, 1993). Furthermore, intravenous sodium-lactate (vasodilator, electrolyte replenisher, and an energetic material for neurons) produced just a trend for enhancing P100 and N100 during a visual semantic categorization task (Kálmán et al., 2005). The only P100 study investigating AChEI effects belongs to Irimajiri et al. (2007). A simple checkerboard stimulation reversal was used in the study and no differences were detected in P100 amplitude or latency values between MCI patients receiving vs. not receiving an AChEI treatment (Irimajiri et al., 2007).

There are several studies investigating the pharmacological effects of the P200 component in ADD patients, most of them with negative results. In those patients, no effect on P200 amplitude or latency was observed in auditory oddball tasks about physostigmine, an AChEI, (Neshige et al., 1988) and donepezil, an AChEI (Lai et al., 2010; Chang et al., 2014). In contrast, intravenous sodium-lactate infusion increased N200 amplitude in ADD patients during a visual semantic categorization task (Kálmán et al., 2005). Given these inconsistent findings and lack of significant effect in some studies, further data are needed covering P100, N100, and P200 components.

3.2. Mid-To Late ERPs and Treatment Effects

3.2.1. N200

Regarding ERP studies investigating pharmacological effects on the N200 component in ADD patients, studies reported no effect of AChEI, physostigmine, or donepezil on N200 amplitude or latency in ADD over CU persons (Neshige et al., 1988; Lai et al., 2010; Chang et al., 2014; Vaitkevičius et al., 2015) or ADD over MCI patients (Lai et al., 2010). Other than cholinergic mechanisms, there is only one study on lactate treatment. Kálmán et al. (2005) used a semantic categorization paradigm in patients with ADD before and after intravenous saline or sodium-lactate infusion. The first ADD group received normal saline, while the second ADD group took sodium lactate. The changes in N200 amplitude were not significant yet demonstrated clear tendencies. The mean amplitude became more negative for the N200 for non-animal responses, with no changes after normal saline infusion. Contrary to its anticipated beneficial effects, these findings may suggest that sodium-lactate fails to significantly improve semantic categorization processes in ADD and this enhancement can be detected by recording ERPs.

Overall, the available pharmacological studies suggest that N200 does not have the required reliability for use in clinical trials due to the limited evidence. Therefore, further studies are necessary to assess treatment effects in the N200 component.

3.2.2. P300

Studies on the treatment effects of cholinergic drugs in ADD on the P300 wave showed decreased latency for a limited period of up to 3 to 6 months in general (Pedroso et al, 2012; Babiloni et al., 2020). Earlier AChEI reports on the effects of physostigmine were noted as increased P300 amplitudes (Dierks et al., 1994) or decreased P300 latency over the short term (Neshige et al, 1988; Katada et al., 2004) in ADD. After the approval of AChEIs in routine ADD treatment, studies on the most commonly used medication donepezil displayed beneficial effects as evidenced by a reduction of P300 latency in ADD during auditory (Reeves et al., 1999; Thomas et al., 2001; Onofrj et al., 2002; Chang et al., 2014), and visual oddball paradigm (Reeves et al., 1999) and rivastigmine reduced P300 latency that was associated with better cognitive performances in mild to moderate probable ADD (Thomas et al., 2001).

Longitudinal P300 studies on the effects of donepezil revealed the latency of the P300 wave is more reliable than the amplitudes (Werber et al., 2003; Parra et al, 2012; Pedroso et al, 2012; Babiloni et al., 2020). Among the five longitudinal P300 studies studying the effects of donepezil or rivastigmine (Thomas et al.,2001; Katada et al., 2003; Lai et al., 2010, Fruehwirt et al., 2019, Vaitkevičius et al., 2015), only one reported unchanged P300 latency or neuropsychological test scores between drug-naive and donepezil-treated ADD groups after monitoring for three months (Vaitkevičius et al., 2015). The effect of AChEIs on the P300 wave improvement in ADD patients was reported as the latency decrease in the first 3 to 6 months of treatment (Thomas et al.,2001; Katada et al.,2003; Lai et al., 2010) or an increase in P300 amplitude (Knott et al., 2002). The progression rates of the P300 wave latency increase in ADD patients on AChEIs were not particularly different in 6 to 12 months (Onofrj et al., 2002; Lai et al., 2010; Fruehwirt et al., 2019) from the patients not using AChEIs (Ball et al., 1989). Similarly, the clinical outcome measures also indicate symptomatic effectiveness of AChEIs as an improvement until 3 to 6 months of treatment. After the improvement, the effectiveness begins to return to the pre-treatment status and continues to decline thereafter (Gauthier et al., 2002; Arai et al., 2016).

Memantine is a commonly used symptomatic add-on medication to cholinergic drugs in ADD. It is an NMDA receptor antagonist and functions as a glutamatergic noncompetitive NMDA receptor antagonist that modulates calcium influx. It has a selective affinity for extrasynaptic NMDAR open channels and does not interfere with normal transmission (Xia et al., 2010). It helps to restore the signal-to-noise ratio in hyper-excited neurons (Chen et al., 1992) and exerts an improving effect on cognitive and sensorimotor functions of Alzheimer's patients (Schmidt et al., 2015). In a meta-analysis for clinical trials of ADD, memantine was found effective for cognition, behavioral disturbance, and activities of daily living (Matsunaga et al., 2015). Regarding the effect of memantine on the P300, there are only two studies in the literature, possibly because memantine is not used alone but mostly given in combination with AChEIs in the treatment regime of ADD. The only ERP study investigating the effects of memantine monotherapy led to a shortening of P300 latency of about 20 ms in 42% of individuals with ADD with no significant change in P300 peak measures at the group level (Kubova et al., 2010). Another study on individuals with ADD with combination therapy of memantine and AChEI found an increase in the latency of P300 at the 12 months of treatment compared to the baseline, suggesting despite cholinergic and memantine treatment, the cognitive EEG parameters worsen in ADD in the long term (Fruehwirt et al., 2019).

Another study assessed the nicotine effect on P300 in two groups of ADD, and nicotine was administered to tacrine-treated and non-treated patients with ADD. Tacrine is the first approved AChEI medication in ADD treatment. Before nicotine administration, tacrine-treated patients displayed shorter auditory P300 latencies than non-treated patients. Acutely administered nicotine did not change auditory P300 but increased the amplitudes of visual P300s in both ADD patient groups. These electrophysiological findings reflected the effects of nicotinic cholinergic processes in ADD (Knott et al., 2002).

Experimental studies indicate that AChEIs drugs increase P300 amplitude in a rat model of AD (Laursen et al., 2014), and decreased amplitudes of ERP components were described in an amyloid-β infused mice model (Kim et al., 2020) or in an animal model of tau overexpression mutations (Nouriziabari et al., 2018). Furthermore, both scopolamine (anticholinergic agent) and entorhinal tau overexpression caused the learning-related changes in the P200 component (Nouriziabari et al., 2018), implying the cholinergic role in the generation of ERPs. The term folate, also known as vitamin B9, refers to a group of water-soluble compounds that play a

fundamental role in a variety of physiologic processes such as regulation of gene expression, neurotransmitter synthesis, and maintenance and repair of the genome (Naderi and House, 2018). In a study assessing the effect of folate with vitamin B12 on P300 in patients with MCI complicated by hyperhomocysteinemia, the MCI group was divided into the intervention group, which was administered with folate, and the control group. After the 24th week, the intervention group had shorter P300 latency than their baseline and the control group. The findings suggest that a decrease in total homocysteine levels at the 24th week may lead to an improvement in the cognitive function of the MCI group revealed by shorter P300 latencies (Jiang et al., 2020).

Other earlier reports exist in the literature studying the treatment effects of other agents including nicergoline and piracetam. Under nicergoline treatment, an ergot alkaloid derivative with a wide spectrum of action, including being a selective alpha-1A adrenergic receptor antagonist, enhancing cholinergic and catecholaminergic neurotransmitter function, and inhibiting platelet aggregation, ADD patients showed decreased P300 latency (Saletu et al., 1995), suggesting an improved vigilance and information processing. On the other hand, piracetam, a nootropic agent with mild antiepileptic properties, plays a role as an AChEI, while also influencing NMDA glutamate receptors, showed no changes in the P300 responses in individuals with ADD (Dabic-Jeftic and Mihula, 1993). Therefore, among the ERP components, the P300 latency might be particularly useful in reflecting cognitive decline and treatment effects in ADD (Lai et al. 2010, Parra et al., 2012; Babiloni et al., 2020). P300 measures may be promising candidates for investigating treatment effects in ADD. Yet, the paucity of studies and small size of participants in the previous P300 studies indicate the necessity of further studies.

3.2.3. Other Late ERP Components

There is only one study investigating the effects of combination therapy (AChEI and memantine) by early and late ERPs (C185, C250, C325, C415, C540) using a number-letter paradigm. In this study, after the baseline ERP data collection, each MCI subject was identified as either having converted to AD or having remained stable according to cognitive state at follow-up assessments. Of the 30 individuals with MCI, 15 patients subsequently progressed to AD and 15 remained cognitively stable. In the group of patients who progressed to AD, 8 of the 15 individuals belonged to the treatment subgroup and seven belonged to the denovo subgroup. Likewise, eight of the 15 patients in the Stable MCI group belonged to the treatment subgroup

and seven belonged to the denovo subgroup. The effects of combination therapy (AChEI and memantine) failed to show any differences in early and late ERPs between the groups (Chapman et al., 2013).

Considering the limited findings in the literature, later ERP components seem not to have the potential to monitor treatment effects in ADD due to not displaying any significant change after interventions. However, further studies are needed to investigate pharmacological effects in memory-related late potentials. The summary of treatment effects on ERP components in patient groups was demonstrated in Table 2.

4. TREATMENT EFFECTS ON EVENT-RELATED OSCILLATIONS (EROs)

4.1. Delta frequency band (<4 Hz)

Treatment effects on delta EROs elicited by visual or auditory oddball tasks in ADD patients demonstrated that delta EROs power is reduced in both AChEI-treated and untreated denovo ADD patients in comparison to CU persons (Yener et al., 2007, 2009). Furthermore, delta ERO long-range connectivity was diminished similarly in ADD patients with or without cholinergic medication (Başar et al., 2010). Therefore, delta EROs seem to be lacking in exhibiting the effect of cholinergic medication in ADD.

4.2. Theta frequency band (4-7 Hz)

Cognitive theta EROs power was similarly reduced in treated and untreated ADD (Yener et al., 2009), whilst ADD patients treated with AChEI medications had an increase in event-related frontal theta phase-locking in comparison to the non-treated ADD group during an oddball task in a cross-sectional study (Yener et al., 2007; Figure 2). So far, there is no longitudinal or cross-sectional EROs study in the literature confirming these medication effects.

Figure 2. The grand averaged waveforms represent reduced visual event-related theta phase-locking in non-treated ADD. The thick black line shows the grand averages of each group to the target stimuli elicited by a classical visual oddball paradigm. The thin gray line demonstrates the average of single sweeps from a single subject (modified from Yener et al., 2007).

4.3. Alpha frequency band (8-12 Hz)

There is only one alpha EROs study investigating treatment effects in patients with ADD. In that study, the alpha EROs coherence was found lower in ADD groups regardless of using AChEI medication. The CU group showed higher values of EROs coherence in the "delta", "theta" and "alpha" frequency bands between left frontoparietal electrode pairs in comparison to both the AChEI-treated ADD and the untreated ADD groups (Başar et al., 2010), implying no effect of cholinergic medication on alpha EROs connectivity.

All these above findings imply that EROs in slow-wave frequency bands, possibly except from theta, are far from showing treatment effects in ADD.

4.4. Beta frequency band (13-30 Hz)

No study reported the results of treatment effects on beta EROs in the ADD so far.

4.5. Gamma Frequency Band (30-45 Hz)

Gamma EROs merit more attention regarding the alterations in both cholinergically treated and untreated (drug-naive) ADD groups indicating a connectivity increase in both ADD subgroups. Interestingly, patients on the cholinergic treatment had further coherence increases than both drug-naive ADD patients and CU persons (Başar et al., 2017). The increase in the long-range (frontoparietal, front-occipital) gamma EROs connectivity in treated and untreated ADD patients were observed in response to visual sensory stimulation, whilst decreased short distance (parieto-occipital) gamma ERO connectivity was noted in treated ADD patients in comparison to drug-naive ADD patients (Başar et al., 2017). This observed pattern consisting of augmented long-range connectivity and a suppressed short-range connectivity fits well with those previously reported on functions of acetylcholine on brain activity (Hasselmo and Sarter, 2011). The mechanism related to increased gamma responses after cholinergic medication may be based on the coexpression of alpha7 nicotinic receptors in GABAergic interneurons (Voytenko et al., 2015) or the change in neuronal excitation/inhibition imbalance observed in AD (Maestu et al., 2021). In brief, gamma ERO connectivity measures seemed to be a promising tool to investigate AChEI treatment in ADD. The summary of treatment effects on EROs in ADD patients is presented in Table 3.

5. OTHER TREATMENT EFFECTS ON ERPs/EROs IN EXPERIMENTAL AND CLINICAL STUDIES

Memantine is a commonly used symptomatic add-on medication to cholinergic drugs in ADD. It is an NMDA receptor antagonist that weakly binds to Mg++ and displays functions that modulate calcium influx. It has a selective affinity for extrasynaptic NMDAR open channels and does not interfere with the normal transmission (Xia et al., 2010), and it helps to restore the signal-to-noise ratio in hyperexcited neurons (Chen et al., 1992). Clinical ERP/ERO EEG studies are scarce on the treatment effects of memantine as it is used as an add-on therapy.

The animal studies investigating the effects of memantine are not redundant in the literature. One of them exploring the effects of memantine using induced EEG elicited by electrical stimuli in anesthetized rats, demonstrated that low dose memantine increased theta and gamma-band activity however, high dose memantine decreased hippocampal theta oscillations (Guadagna et al., 2012). A study on freely moving mice by Ma et al. (2015) showed the LTP-enhancing effect of memantine that was blocked by the injection of scopolamine, an anticholinergic drug, indicating an interplay between cholinergic and glutamatergic antagonists favoring cognitive improvement. Memantine significantly increased gamma oscillations in freely moving animals (Hiyoshi et al., 2014; Ahnaou et al., 2014; Ma et al., 2015).

Other medications such as semagacestat, a gamma-secretase inhibitor that reduces the production of amyloid-β, cause decreased hippocampal theta oscillatory activity induced by electrical stimuli in anesthetized mice (Hajos et al., 2013). On the other hand, piracetam, a nootropic agent, increased hippocampal theta oscillations that are induced by electrical stimuli in anesthetized rats (Kinney et al., 1999). The treatment effects of animal studies for EEG-ERP/EROs in AD models are presented in Table 4.

In brief, experimental studies of induced EEG investigating the effects of AChEIs and memantine reported an increase in the power of theta and gamma bands (Ahnaou et al., 2014). A few clinical studies investigating the effects of AChEIs on EROs in medicated ADD patients compared to unmedicated ADD patients can be summarized as improvement of frontal theta phase-locking and altered gamma ERO connectivity. Yet, these results await to be confirmed by other clinical research groups.

General rules of oscillatory activity imply a potential for modulating brain waves by resetting the oscillatory hierarchy such as 1) amplitude periodicity of the faster waves matches with those of slower waves (Amzica and Steriade, 2000; Vanhatalo et al., 2004), 2) amplitude of gamma oscillation depends on theta oscillation phase (Buzsaki et al., 2003) and a variety of cross-frequency couplings occurs between frequency bands, such as those between beta-gamma or theta-alpha bands during working memory paradigms (Siebenhühner et al., 2016), and 3) ongoing cortical activity exerts an effect on the processing of a stimulus (Başar et al., 1980; Polich, 1997; Fries et al., 2001; Babiloni et al., 2006).

Hence, a new avenue for ADD treatment is open to neuromodulation techniques including, transcranial alternating current stimulation (TACS), transcranial direct current stimulation (TDCS), transcranial magnetic stimulation (TMS), training to enhance oscillations in alpha and beta bands for higher memory performance and gamma-band for depression (Escolano et al., 2014) and neurofeedback in ADD (Luijmes et al., 2016; Sürmeli et al., 2016; Jiang et al., 2017). TDCS is a technique to modulate brain oscillations by applying a direct electrical current to the scalp. In a study on individuals with ADD and CU persons using TDCS, the result favored beneficial effects of the intervention, such as increased amplitudes of P200 and P300 and increased frontal theta EROs within a 150-300 ms time window (Cespón et al., 2019).

Brain stimulation techniques may help to reduce brain hyperexcitability reported in MCI or ADD (Adaikkan et al., 2019; for review, see Toniolo et al., 2020). Many studies performed on ADD/MCI patients using these techniques aimed to reduce hyperexcitability of the brain by transcranial magnetic stimulation (Koch et al 2018; Arendash et al., 2019; Sabbagh et al., 2019), or by tDCS (Khedr et al., 2019; Ferrucci et al., 2008; by tACS (Xing et al., 2020) or by 40 Hz sensory stimulation (Cimenser et al, 2021; Ismail et al., 2018) or photobiomodulation (Chao, 2019).

Recently, there has also been a focus on various types of exercise including aerobic, strengthening, and combined involvements as another non-pharmacological intervention that is associated with cognitive improvement. Using different cognitive tasks, it was suggested that involvement in physical or aerobic exercise appears to be related to increased amplitude and/or decreased latency of P300 in young and older active CU persons compared to individuals with a sedentary lifestyle (for a review, see Huang et al., 2016). In MCI patients, it was reported that

either aerobic dance routines demonstrated decreased P300 latency (Zhu et al., 2018), or MCI who participated in two different types of exercise programs displayed an increase in P300 amplitudes (Tsai et al., 2018, 2019). Another longitudinal study showed that both physical exercise programs and social-gathering intervention resulted in an improvement in P300 parameters (Pedroso et al., 2018). The findings above indicate that P300 measures are possible candidates to be used in non-pharmacological treatment studies.

In the current paper, a literature review was not performed for this section; however, it is worth reminding that current brain stimulation studies in ADD as a non-pharmacological intervention may constitute an important avenue for investigating treatment effects on ERPs/EROs.

6. DISCUSSION

In the current article, a multidisciplinary panel of experts reviewed the literature about the effects of medications or interventions on ERO/ERP EEG oscillations during cognitive tasks. The literature on this subject seems to be too scarce to provide definitive answers. Among the most used symptomatic treatment of ADD, cholinergic drugs lead to a reduction in latency of P300 and an increase in amplitudes of late ERPs components (N200, P300) temporarily for up to a year. Effects of cholinergic medications on EROs can be summarized as an increase in theta phase-locking and gamma connectivity, yet further confirmation is needed. Effects of memantine, another licensed symptomatic medication acting as an NMDA receptor antagonist for the treatment of ADD, have not been well studied on ERPs/EROs in ADD, possibly due to its common use as an add-on medication to cholinesterase inhibitors. Animal studies confirmed that cholinesterase inhibitors cause increased amplitudes of P300 like ERPs and increased levels of induced theta and gamma oscillations.

Even though there have not been many new options of treatment in the past two decades, possibly disease-modifying drugs are becoming available for ADD. Many questions remain to be answered and cannot be covered by previous literature. The current paper studying ERP/ERO EEG studies revealed that P300 measures are the most promising ERP components, whilst theta and gamma ERO responses may bear a potential for monitoring treatment effects in drug trials or intervention studies in ADD. To our knowledge, there has been no data assessing treatment effects on N170, N230, VPP, LPP, N400, and P600 components of ERPs while the current

literature covers limited information on the delta, theta, alpha, and gamma EROs in patients with ADD or MCI. Therefore, further studies are needed to cover these components for the evaluation of medication effects.

The medications which are used to enhance cognitive functions, both in patients with ADD and MCI and CU individuals, work through ACh neurotransmission. ACh is closely involved in synaptic transmission and the formation of memories and the performing of cognitive tasks. It was reported that donepezil, rivastigmine, or galantamine had good results in enhancing cognitive performance in patients with mild to moderate ADD when compared with placebo (Birks et al., 2006). However, diverse studies with CU individuals indicated that AChEIs slightly improve verbal memory after semantic processing of words, attention memory, information processing, executive function, and memory (Repantis et al., 2010). Secondly, memantine is an agent used to treat moderate to severe AD. It acts on the glutamatergic system by antagonizing N-methyl-d-aspartate (NMDA) receptors. This drug has been shown to slightly improve cognitive functions as monotherapy for ADD (Matsunaga et al., 2015). There are also few studies about the cognitive-enhancing capacity of memantine on CU individuals (Juarez-Portilla et al., 2018). Considering these findings, it can be summarized that a great deal of the EEG potentials and oscillations demonstrated limited medication effect in the literature since the effects of currently registered medications on cognition are minor and short-lived. In the future, EEG related methodologies may help to uncover the changes in the brain activity in response to remedies such as newly developed anti-amyloid, anti-tau, or hybrid remedies (for reviews, see Cummings et al., 2021; Tomlo et al., 2020; Zagórska and Jaromin, 2020). The concurrent investigation of ERPs/EROs methodologies and other well-studied valid biomarkers in at-risk ADD patients may help validate the EEG methodologies to monitor the effects of treatment on brain functions. Furthermore, additional use of ERP/EROs to the rsEEG activity may offer an advantage for observing the treatment effects of ADD, as gathered from limited numbers of comparative electrophysiological studies with small numbers of participants in the literature (Olichney et al., 2002b; Van der Hiele et al., 2007; Deiber et al., 2009; Lopez et al., 2014; Jovicich et al. 2019).

EEG methodologies assessing treatment effects can be useful for personalized medicine. Even though a wide range of variability in the accuracy rates of ERPS/EROs limits their use on an individual basis for diagnostic purposes in the ADD, the possibility is higher when the

treatment effect is considered, as each person can provide control of themselves before treatment. At that point, ERPs/EROs may offer advantages for monitoring intervention or treatment effects, because these electrophysiological methods provide almost an individualistic electrophysiological signature (Näpflin et al., 2008), and indicate an alteration about 10 to 30% to the baseline of the same individual which is much higher rate than any other neuroimaging marker elicits (Olichney and Hillert, 2004; Başar et al., 2013).

Significant limitations of this article include (i) the restrictive criteria used for the review of literature; (ii) the inclusion of studies using various diagnostic criteria for AD in the era without current diagnostic research criteria, and (iii) the included patient groups may not exclude AD patients with vascular changes in brain, TDP-43 related hippocampal impairment, and Lewy body pathology; (iv) the use of the term MCI to describe amnestic MCI patients, thus considering possible prodromal ADMCI without in-vivo biomarkers of ADD that were not existent in earlier studies; (v) nonhomogeneous procedures for the artifact detection in EEG analyses. Moreover, a variety of analyses and paradigms limit the use of ERPs/EROs along with lower rates of compliance of patients during the recordings. The need for the participant- or user-friendly paradigms is paramount, as well as the standardized and harmonized procedures for the acquisition and analyses of ERPs/EROs.

7. CONCLUSIONS

The ERP components or event-related EEG oscillations for investigating treatment effects remain to be an unexplored field. The current diagnostic research criteria work-up for ADD described by the Working Group of the National Institute of Aging and Alzheimer's Association (NIA-AA) Research Framework (Jack et al., 2018) do not include EEG measures as those for DLB (McKeith et al., 2020). As earlier studies on event-related EEG measures consistently show association with atrophy in structural MRI or disease progression in AD, they can be considered as reflecting neurodegeneration occurring in the disease course. Furthermore, keeping in mind the low rates of accessibility to the currently validated AD biomarkers, the present Expert Panel posits not only introducing the event-related EEG measures as a physiological biomarker (i.e., "P" biomarker) into A-T-N Research Framework (Jack et al., 2018) but also using them to explore treatment effects in AD spectrum. These electrophysiological biomarkers may probe mechanisms of thalamocortical and subcortical

neural (de)synchronization about treatment effects. For the current study on treatment effects, the biomarkers of ERP/ERO EEG markers may be represented by the mentioned P300 component and theta and gamma ERO measures during oddball tasks.

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Conflict of Interest

There are no relevant conflicts of interest for the co-authors in the present article.

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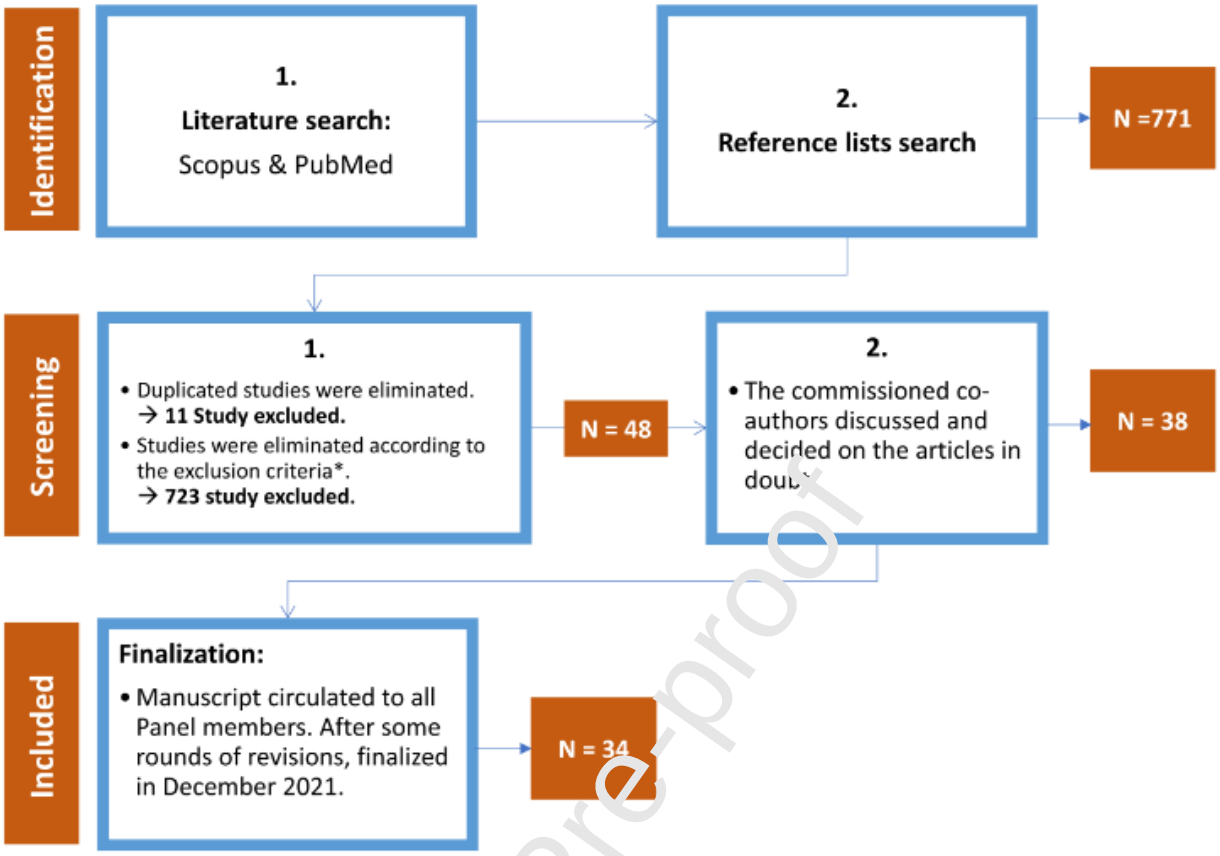

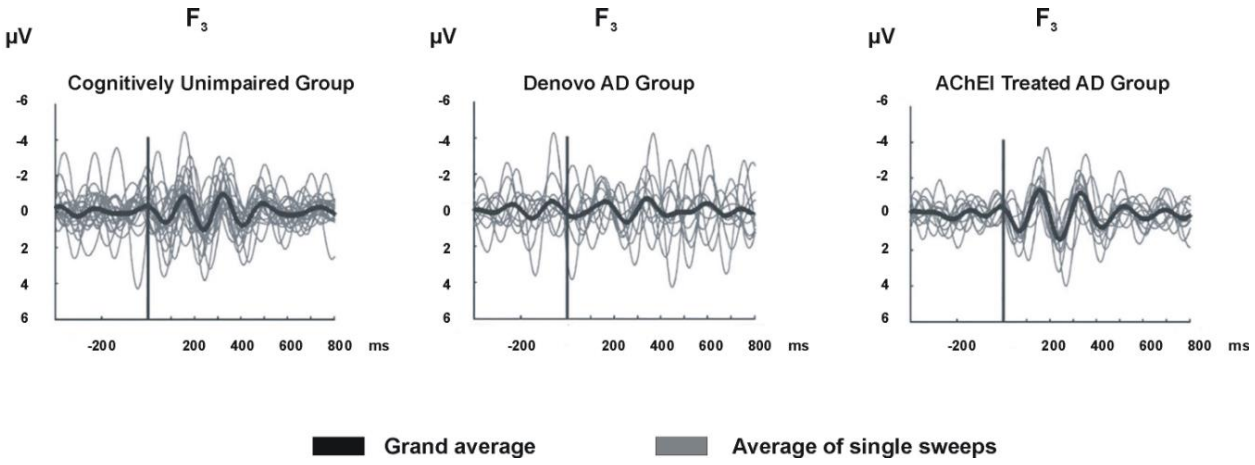

Table 1. ERP waves, their functions, and possible generators

EARLY (Sensory components)
● N100 (N1) is involved with primary perceptual processing of incoming information and early attentional allocation to visual stimuli (Lijffijt et al., 2009). ● P100 (P1) is a positive wave elicited by different types of visual stimuli only and considered to be related to early visual processing (Heinze and Mangun, 1994). ● P200 (P2) is associated with early attentional allocation to visual stimuli and is involved with primary perceptual processing of incoming information (Omoto et al., 2010). ● N170 appears as a negative peak over parieto-occipital regions and is related to bottom-up perceptual processing of faces in the area of occipito-temporal cortex (Feuerriegel et al., 2015).
MID or LATE (Cognitive components)
● N200 is considered to reflect selective attention and conscious discrimination, so it is associated with information processing, but not necessarily with memory performance (Howe et al., 2014). Possible generators of the N200 include the reticular formation, frontal cortex, centro-parietal cortex thalamus and lemniscus, inferior colliculus, hippocampus, frontocentral cortical areas (Vaitkevičius et al., 2015). ● VPP (vertex positive potential) is a positive peak over fronto-central regions within a similar N170 time frame. It is related to bottom-up perceptual processing of faces in the area of the occipito-temporal cortex; it was also reported to reflect an integration of top-down and bottom-up visual processing (Lu et al., 2017). ● P300 (P3b) is related to discrimination between target and standard stimuli that engages focused attention and decision making, or working memory demanded by task (Polich, 1989, 1997; Posner and Petersen, 1990; Pardo et al., 1991; Başar-Eroğlu et al., 1992; Posner, 1992; Huang et al., 2015). P3a and P3b constitute the subcomponents of P300. P3a is generated when stimuli are processed if sufficient attentional focus is engaged. P3b occurs when subsequent attentional resource activations promote memory functions in temporal-parietal areas (Polich, 2007). In brief, reverberating circuits between frontal-parietal and temporal cortical regions and possibly their

connections with limbic structures take a role in the generation of the P3 potential (Knight, 1990; Soltani and Knight, 2000; Rektor et al., 2004).

- N400 refers to a negative component in the average ERP that reaches its peak amplitude approximately 400 ms after stimulus onset and is associated with linguistic and semantic processing (Olichney et al., 2006, 2008, 2011). N400 generators are bilaterally anterior fusiform and parahippocampal gyri (Olichney and Hillert, 2004).
- P600 (LPC) is a positive deflection with a centro-parietal peak at approximately 600 ms. In language studies, the P600/LPC, also known as the 'Syntactic Positive Shift', has been linked to a wide range of disagreements in syntactic rules (Kuperberg, 2007). P600 generators are median temporal lobe and paralimbic cortical regions (Katada et al., 2004; Kimiskidis and Papaliagkas, 2012).

(For further information related to ERP/EROs reviews please see, Paitel et al., 2021; Rossini et al., 2020; Tarawneh et al., 2020; Horvath et al., 2018; Morrison et al., 2019; Palop and Mucke, 2016; Seer et al., 2016; Feuerriegel et al., 2015; Hedges et al., 2016; Huang et al., 2015; Nimmrich et al., 2015; Güntekin and Başar, 2014; Howe et al., 2014; Howe, 2014; Tsolaki et al., 2014; Başar, 2012; Başar and Güntekin, 2008, 2012, 2013; Yener and Başar, 2010, 2013; Farwell et al., 2012; Kimiskidis and Papaliagkas, 2012; Rêgo et al., 2012; Yamasaki et al., 2012; Drago et al., 2011; Lizio et al., 2011; Vecchio and Määttä, 2011; Jackson and Snyder, 2008; Sauseng and Klimesch, 2008; Uhlhaas and Singer, 2008; Rossini et al. 2007; Prichep et al., 2005; Herrmann and Demiralp, 2005; Polich and Corey Bloom, 2005; Katada et al, 2004; Olichney and Hillert, 2004; Başar-Eroğlu et al., 2001; Klimesch., 1999; Başar-Eroğlu and Demiralp, 1991; and for hypotheses and rules for EROs, the following articles have been recommended; Hebb et al 1949; Başar-Eroğlu et al., 1991, 1992, 2001; Schürmann et al., 1997; Sakowitz et al., 2001).

Table 2. Treatment effects on ERP components in patient groups

Reference	Participants	Treatment	Amplitude Change	Latency Change
P300 studies with Oddball task				
Jiang et al. (2020)	MCI with hyperhomocysteinemia (n=92) - Intervention group (N=46)	Folate & Vit B12 (24 weeks)	↔	↓
Fruehwirt et al. (2019)	Possible and probable ADD (n=63)	Constant vs. variable dose of medication (AChEI and memantine) (N=39)		↔ in constant versus variable dementia medication. ↑ in ADD at 18 months.
Vaitkevičius et al. (2015)	De-novo-ADD (ADD-N, n=22) Treated-ADD (ADD-T group, n=22)	Donepezil for 3 months	↔ ADD-N=ADD-T	↔ ADD-N=ADD-T

	CU (n=50)			
Chang et al. (2014)	ADD (n=100) CU (n=20)	Donepezil for 23 weeks.	↔ ADD after donepezil.	↓ ADD after the treatment.
Kubová et al. (2010)	ADD (n=17)	Memantine (de novo to post-treatment 6 months follow-up)		↔ post-treatment at group level. ↓ about 20 milliseconds in 42% of patients.
Lai et al. (2010)	ADD (n=20) Denovo MCI(n=18) CU (n=14)	Donepezil; - Baseline - 1 year follow-up	↔ in baseline and follow-up assessments among groups.	↑ ADD > MCI > HC
Werber et al. (2003)	Patients with dementia (n=32) -ADD	AChEIs (Tacrine, Donepezil, Rivastigmine)	↔ after the treatment. ↔	↓ in dementia patients after the treatment.

	(n=14) -PDD (n=10) -Vascular dementia (VD) (n=8)		between subgroups of dementia.	↔ between subgroups of dementia.
Katada et al. (2003)	ADD (n=14)	Donepezil		↓ after 1 month treatment. ↑ at 6 months compared with follow-up at 1 month.
Onofrj et al. (2002)	Mild ADD (n=30) Moderate-severe ADD (n=30) CU (n=40)	Donepezil for 6 months Vitamin E for 6 months; - Group I Donepezil with "mild" ADD (N=15) - Group I		↓ reduced in both mild and moderate-to-severe ADD groups, after the treatment. ↑ in both mild and moderate-to-severe ADD groups, after Vitamin E treatment.

		Vitamin E with "mild" ADD (N=15) - Group II Donepezil with "moderate-severe" ADD (N=15) - Group II Vitamin E with "moderate-severe" ADD (N=15)		
Thomas et al. (2001)	ADD (n=60) CU (n=60)	Throughout 26 weeks; - Treated-ADD with donepezil (n=20) - Treated-ADD with vitamin E		↑ in the vitamin E-treated ADD patients. ↓ in both donepezil-treated and Riv-treated patients.

		(n=20) - Treated-ADD with rivastigmine (Riv) (n=20)		
Reeves et al. (1999)	ADD (n=12)	Donepezil treatment for 1 month	↔ between baseline assessment and after 1-month treatment.	↓ after the 1-month donepezil treatment.
Oishi et al. (1998)	ADD (n=10)	The traditional Chinese medicine for 3 months (astragalus root, Prunella vulgaris, pueraria root, Lycii fructus, cnidium rhizome, rhubarb,		↓ after the treatment.

		alisma rhizome, peach kernel, ginseng, oyster shell)		
Saletu et al. (1995)	Senile dementia of the AD type (n=56) -28 treated with nicergolineADD/NIC -28 placebo-AD/PLAC Multi-infarct dementia (MID) (n=56) -28 treated with nicergoline-MID/NIC -28 placebo-MID/PLAC	The nicergoline (Sermion) for 8 weeks		↓ in both ADD/NIC and MID/NIC groups after the treatment. ↓ lengthened in both ADD/PLAC and MID/PLAC groups after the treatment.
Dierks et al. (1994)	Younger CU male (n=6)	Physostigmine for the	↑ 1 hour after application of	↔ 1 hour after application of

	(treated with physostigmine and biperiden) Elderly CU (n=10) (treated with pyritinol)	first day and biperiden for the second day Pyritinol	*physostigmine*. ↓ 1 hour after application of *biperiden*. ↑ after application of *pyritinol*.	*physostigmine*. ↑ 1 hour after application of *biperiden*. ↔ after application of *pyritinol*.
Dabic-Jeftic and Mikula (1993)	ADD (n=7) Multi-infarct dementia (MID) (n=15) CU	Piracetam for 3 months	↓ in patients with ADD and MID compared to CU individuals.	↑ in patients with ADD and MID compared to CU individuals.
Neshige et al. (1988)	ADD (n=13) MID (n=14) CU (n=9)	Physostigmine - Treated-ADD (n=5) - Treated-MID (n=5)	↔ among groups.	↑ in patients with ADD and MID compared to CU individuals. ↓ in 6 among 10 patients who received physostigmine. ↑ in one

				MID patient.
P300 study with Continuous Performance task				
Knott et al. (2002)	ADD (n=13)	Acute nicotine treatment; - Treated with tacrine (n=6) - Denovo ADD (n=7)	↑ in tacrine-treated group with visual paradigm with no difference detected with auditory paradigm at post-nicotine administration.	↑ in tacrine-treated group compared to non-treated group at pre-nicotine administration.
P200 studies with Oddball task				
Chang et al. (2014)	ADD (n=100) CU (n=20)	Donepezil for for 23 weeks.	↔ ADD after the treatment.	↔ ADD after the treatment.
Lai et al. (2010)	ADD (n=20) Denovo MCI(n=18) CU (n=14)	Donepezil; - Baseline - 1 year follow-up	↔ at baseline and follow-up assessments.	↔ at baseline and follow-up assessments.
Neshige et al. (1988)	ADD (n=13)	Physostigmine	↔ among groups.	

	MID (n=14) CU (n=9)	- treated-ADD (n=5) - treated-MID (n=5)		
P200 study with Categorization task				
Kalman et al. (2005)	Denovo ADD (n=13) Treated-ADD (n=13)	Intravenous sodium-lactate	↑ related to the positivity in the mean amplitudes after the lactate treatment.	
P100 study with Visual Checkerboard Stimulation				
Irimajiri et al. (2007)	Treated-MCI (n=8) Denovo MCI (n=7) CU (n=15)	AChEIs; (donepezil, rivastigmine, galantamine)	↔ among groups.	↔ among groups.
N100 studies with Oddball task				
Chang et al. (2014)	ADD (n=100) CU (n=20)	Donepezil for for 23 weeks.	↔ after the treatment.	↔ after the treatment.
Lai et al. (2010)	ADD (n=20) Denovo MCI(n=18)	Donepezil; - Baseline	↔ at baseline and follow-up assessments.	↔ at baseline and follow-up assessments.

	CU (n=14)	- 1 year follow-up		
Dabic-Jeftic and Mikula (1993)	ADD (n=7) Multi-infarct dementia (MID) (n=15) CU	Piracetam for 3 months		↓ in patients with ADD.
Neshige et al. (1988)	ADD (n=13) MID (n=14) CU (n=9)	Physostigmine - treated-ADD (n=5) - treated-MID (n=5)	↔ among groups.	↔ among groups.
N100 study with Categorization task				
Kalman et al. (2005)	Treated-ADD (n=13) Denovo ADD (n=13)	Intravenous sodium-lactate	↑ related to the positivity in the mean amplitudes after the lactate treatment.	
N100 study with Continuous Performance task				
Knott et al. (2002)	ADD (n=13)	Acute nicotine treatment;	↔ at pre- and post-nicotine administration.	↔ at pre- and post-nicotine administration.

		- ADD treated with tacrine (n=6) - Non-treated ADD (n=7)		
N200 studies with Oddball task				
Vaitkevičius et al. (2015)	Treated-ADD (ADD-T group) (n=22) Denovo ADD (ADD-N) (n=22) CU (n=30)	Donepezil for 3 months		↑ ADD-T>ADD-N
Chang et al. (2014)	ADD (n=100) CU (n=20)	Donepezil for for 23 weeks.	↔ after the treatment.	↔ after the treatment.
Lai et al. (2010)	ADD (n=20) Denovo MCI(n=18) CU (n=14)	Donepezil; - Baseline - 1 year follow-up	↔ at baseline and follow-up assessments.	↔ at baseline and follow-up assessments.

Neshige et al. (1988)	ADD (n=13) MID (n=14) CU (n=9)	Physostigmine - treated-ADD (n=5) - treated-MID (n=5)	↔ after the treatment.	↔ after the treatment.
N200 study with Categorization task				
Kalman et al. (2005)	Treated-ADD (n=13) Denovo ADD (n=13)	Intravenous sodium-lactate	↑ after the lactate treatment, the mean amplitude became more negative, however changes were not significant. ↔ after normal saline infusion.	
Other late components (C185, C250, C325, C415, C540)				
Chapman et al. (2013)	MCI (n=30)	AChEIs and memantine	↔ no difference in post-treatment	↔ no difference in post-treatment

	-MCI subjects converted to ADD (n=15) -Treated converted subgroup (n=8) -Denovo converted subgroup (n=7) Stable MCI (n=15) -Treated stable subgroup (n=8) -Denovo stable subgroup (n=7)		parameters during number-letter paradigm.	parameters during number-letter paradigm.

Table 3. Treatment effects on EROs during simple light stimulation and oddball paradigm in patients with ADD

Reference	Participants	Amplitude Change
Event-Related Delta Oscillations		
Yener et al. (2012)	Mild ADD(n=34); -Denovo ADD (n=17) -ADD treated with AChEIs (n=17) CU (n=17)	↓ maximum peak-to-peak amplitudes of treated and denovo ADD groups compared to CU.
Başar et al. (2010)	Mild probable ADD (n=38); -Denovo ADD (n=19) -ADD treated with AChEIs (n=19) CU (n=19)	↓ coherences in treated and denovo ADD compared to CU. ↔ no treatment effects in coherence values between groups.
Yener et al. (2009)	ADD (n=22) -Denovo ADD (n=11) -ADD treated with AChEIs (n=11) CU (n=19)	↔ no treatment effects during simple light stimulation.
Güntekin et al. (2008)	Mild probable ADD (n=21) -Denovo ADD (n=10) -ADD treated with AChEIs (n=11) CU (n=19)	↔ no treatment effect between groups. ↑ coherence in CU individuals compared to treated and denovo ADD.
Yener et al. (2008)	Mild probable ADD (n=22); -Denovo (n=11) -ADD treated with AChEIs (n=11) CU (n=20)	↔ no treatment effect between groups. ↓ maximum peak-to-peak amplitudes of ADD regardless of AChEI treatment.
Event-Related Theta Oscillations		
Başar et al. (2010)	Mild probable ADD (n=38); -Denovo ADD (n=19) -ADD treated with AChEIs (n=19) CU (n=19)	↓ coherences in treated and denovo ADD compared to CU. ↔ no treatment effects in coherence values between groups.
Yener et al. (2009)	ADD (n=22) -Denovo ADD (n=11) -ADD treated with AChEIs (n=11) CU (n=19)	↑ in denovo ADD during simple light stimulation compared to treated ADD and CU groups.
Güntekin et al. (2008)	Mild probable ADD (n=21); -Denovo ADD (n=10), -ADD treated with AChEIs ADD (n=11)	↔ no treatment effect between groups. ↓ coherences in treated and denovo ADD groups compared to CU individuals.

	CU (n=19)	
Yener et al. (2007)	ADD (n=22); -Denovo ADD (n=11) -Treated ADD (n=11) CU (n=20)	↑ phase-locking in treated ADD compared to denovo ADD. ↓ phase-locking in denovo ADD compared to CU. ↔ phase-locking values between treated ADD and CU persons.
Event-Related Alpha Oscillations		
Başar et al. (2010)	Mild probable ADD (n=38); -Denovo ADD (n=19) -ADD treated with AChEIs (n=19) CU (n=19)	↓ coherences in treated and denovo ADD compared to CU. ↔ no treatment effects in coherence values between groups.
Yener et al. (2009)	ADD (n=22) -Denovo ADD (n=11) -ADD treated with AChEIs (n=11) CU (n=19)	↔ no treatment effects during simple light stimulation.
Güntekin et al. (2008)	Mild probable ADD (n=21); -Denovo ADD (n=10), -ADD treated with AChEIs (n=11) 19 CU	↑ coherences in treated ADD compared to denovo ADD group. ↑ coherence values in CU persons compared to denovo ADD group. ↔ between CU and treated ADD.
Event-Related Beta Oscillations		
Başar et al. (2010)	Mild probable ADD (n=38); -Denovo ADD (n=19) -ADD treated with AChEIs (n=19) CU (n=19)	↔ no treatment effects in coherence values between groups.
Event-Related Gamma Oscillations		
Başar et al. (2017)	Mild probable ADD (n=39); -Denovo ADD (n=21) -ADD treated with AChEIs (n=18) CU (n=21)	During both simple light stimulation and oddball paradigm; ↑ coherences at fronto-parietal areas in treated ADD compared to denovo patients. ↑ coherences over occipital-parietal electrodes in denovo compared to treated ADD patients.

Başar et al. (2010)	Mild probable ADD (n=38); -Denovo ADD (n=19) -ADD treated with AChEIs (n=19) CU (n=19)	↔ no treatment effects in coherence values between groups.
Yener et al. (2009)	ADD (n=22) -Denovo ADD (n=11) -ADD treated with AChEIs (n=11) CU (n=19)	↔ no treatment effects during simple light stimulation.

Table 4. The treatment effects of animal studies for ERP/EROs in AD

References	Participants	Treatment	Task	ERP component	Results
Kim et al. (2020)	12 Aβ-infused mice model (Aβ group) 7 normal mice model (vehicle group)	Aβ-infusion	Auditory oddball paradigm	P100 N100 P200	The ↓ difference of ERP responses between standard and deviant tones in the Aβ-infused mice group. The ↓ difference of N1 component between standard and deviant tones in the parietal region in the Aβ-infused group.
Nouriziabari et al. (2018)	4 group of 12 rats; -Saline-treated, GFP expressing -Saline-treated, tau-expressing -Scopolamine treated, GFP expressing -Scopolamine treated, tau-expressing	Scopolamine hydrobromide treatment	Trace eyeblink conditioning paradigm	P100 P200 P300 N100 N200	Scopolamine caused the learning-related changes in the temporal P2 component and other learning-unrelated components in three locations. Entorhinal tau overexpression primary affected the amplitude of temporal visual ERPs and learning-unrelated frontal and temporal auditory ERP components.
Laursen et al. (2014)	21 Sprague Dawley rats; -10 animals infused 1.25 µg IgG-192-SAP -11 animals sham-lesioned	Donepezil hydrochloride	Auditory oddball paradigm	P300	↓ amplitude in SAP-lesioned rats compare to sham-lesioned rats. ↑ amplitude in SAP-treated rats after the treatment.

	with sterile PBS				
Guadagna et al . (2012)	Anesthetized mice	Memantine	Induced EEG activity by electrical stimulation and spontaneous EEG		Dose dependent alteration in induced theta activity in hippocampus; ↑ in low dose ↓ in high dose ↔ in spontaneous theta rhythms. ↑ in spontaneous and induced-gamma power.
Hajos et al. (2013)	Anesthetized mice	Semagacestat (a gamma secretase inhibitor reducing amyloid-β)	Induced EEG activity by electrical stimulation and spontaneous EEG		↓ induced-theta activity in hippocampus.
Kinney et al. (1999)	Anesthetized rats	Piracetam (a nootropic agent)	Induced EEG activity by electrical stimulation		↑ induced-theta activity in hippocampus.
Kinney et al. (1999)	Anesthetized rats	Apamin (a potassium channel blocker)	Induced EEG activity by electrical stimulation		↑ induced-theta activity in hippocampus.

HIGHLIGHTS

- The multidisciplinary expert panel aimed to review the effects of medications on ERO/ERP EEG oscillations in patients with ADMCI and ADD.
- Treatment effects were mostly pronounced in the ERP P300 component along with theta and gamma ERO measures.
- Electrophysiological markers may probe mechanisms of thalamocortical and subcortical neural (de)synchronization related to treatment effects.