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Are there consistent abnormalities in event-related EEG oscillations in patients with Alzheimer's disease compared to other diseases belonging to dementia?

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Abstract

Cerebrospinal and structural-molecular neuroimaging in-vivo biomarkers are recommended for diagnostic purposes in Alzheimer's disease (AD) and other dementias; however, they do not explain the effects of AD neuropathology on neurophysiological mechanisms underpinning cognitive processes. Here, an Expert Panel from the Electrophysiology Professional Interest Area of the Alzheimer's Association

Electrophysiology Professional Area (EPIA), ISTAART https://action.alz.org/personifyebusiness/Membership/ISTAART/PIA/Electrophysiology.aspx.

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reviewed the field literature and reached consensus on the event-related electroencephalographic oscillations (EROs) that show consistent abnormalities in patients with significant cognitive deficits due to Alzheimer's, Parkinson's (PD), Lewy body (LBD), and cerebrovascular diseases. Converging evidence from oddball paradigms showed that, as compared to cognitively unimpaired (CU) older adults, AD patients had lower amplitude in widespread delta (>4 Hz) and theta (4–7 Hz) phase-locked EROs as a function of disease severity. Similar effects were also observed in PD, LBD, and/or cerebrovascular cognitive impairment patients. Non-phase-locked alpha (8–12 Hz) and beta (13–30 Hz) oscillations were abnormally reduced (event-related desynchronization, ERD) in AD patients relative to CU. However, studies on patients with other dementias remain lacking. Delta and theta phase-locked EROs during oddball tasks may be useful neurophysiological biomarkers of cognitive systems at work in heuristic and intervention clinical trials performed in AD patients, but more research is needed regarding their potential role for other dementias.

KEYWORDS

Alzheimer's disease mild cognitive impairment (ADMCI), Alzheimer's disease (AD), event-related desynchronization, event-related oscillations (EROs), event-related potentials (ERPs), event-related synchronization, lewy body dementia (LBD), Parkinson's disease (PD), vascular cognitive impairment (VCI)

1 | BACKGROUND

1.1 | The gap in Alzheimer's disease (AD) biomarkers

Alzheimer's disease (AD) is one of the most diffuse neurodegenerative disorders characterized by a progressive cognitive decline to dementia. Several biomarkers of AD are currently used in clinical research. According to the US National Institute on Aging–Alzheimer's Association (NIA-AA), in-vivo cerebrospinal fluid (CSF) measures of Abeta and phoshpo tau and amyloid/tau positron emission tomography (PET) maps allow the diagnosis of AD at the preclinical, prodromal (with objective mild cognitive impairment, MCI), and overt dementia stages for clinical trials (Albert et al., 2011; Jack et al., 2018; McKhann et al., 2011). Furthermore, AD progression may be monitored by biomarkers derived from 18Fluorodeoxyglucose PET (FDG-PET), total tau in CSF, and magnetic resonance imaging (MRI) of brain atrophy in temporoparietal cortex and the medial temporal lobes (including the hippocampi).

Apart from the indirect role played by FDG-PET as a sensitive marker of neural and synaptic integrity, none of the above biomarkers reflects effects of AD neuropathology on neurophysiological mechanisms underpinning cognitive processes. To fill this gap, measures of scalp-recorded electroencephalographic (EEG) rhythms are promising as they are non-invasive, cost-effective, and based on recording techniques largely available worldwide, including lower- and middle-income countries (Babiloni, Barry, et al., 2020; Babiloni, Blinowska, et al., 2020; Rossini et al., 2020). These EEG measures may probe the effects of AD on ascending activating systems and reciprocal thalamus-cortical circuits in which oscillatory (de)synchronizing signals underpin cortical arousal during quiet vigilance and sensory processing in cognitive-motor tasks (Babiloni, Barry, et al., 2020; Babiloni, Blinowska, et al., 2020; Pfurtscheller and Lopes da Silva, 1999; Rossini et al., 2020).

In AD patients, abnormalities in event-related EEG rhythms may reflect the effect of AD neuropathology on (1) the synchronous conduction of action potentials along neural networks in multiple cortical areas and (2) synaptic transmissions, thus affecting spatial and temporal summation of post-synaptic potentials in cortical pyramidal neurons and, consequently, scalp-recorded EEG activity (de Haan et al., 2009; Pfurtscheller and Lopes da Silva, 1999; Pievani et al., 2011; Stam et al., 2007; Teipel et al., 2016). Animal studies have elucidated the cellular and molecular basis of these effects at cortical and subcortical levels as loss of myelinated axons possibly associated with cortical neural hyperexcitability and hypersychronization as well as reduced neurotransmission, neural signaling, and synaptic activity (Crunelli et al., 2015; Steriade, 1993).

Resting state eyes-closed EEG rhythms in quiet vigilance have been repeatedly investigated in AD patients as candidate biomarkers in clinical trials (for reviews, see Babiloni et al.,

2021; Babiloni, Blinowska, et al., 2020; Rossini et al., 2020). The most consistent findings from this research indicates that AD patients with MCI and dementia show abnormalities in peak frequency, power, and "interrelatedness" at posterior alpha (8–12 Hz) and widespread delta (<4 Hz) and theta (4–8 Hz) rhythms according to disease progression (Babiloni et al., 2021).

1.2 | Phase- and non-phase-locked event-related EEG oscillations

Another well-known application of the EEG technique in AD patients allows for the study of EEG activity phase-locked to sensory stimuli or participant responses during cognitive tasks, the so-called event-related potentials or ERPs (Babiloni, Blinowska, et al., 2020). It is well known that ERPs are obtained by averaging voltages across artifact free EEG epochs related to all sensory stimuli or participant responses using the stimulus or response onset as a zerotime. This method allows for the removal of neural processes that are not phase-locked to sensory stimuli during the EEG recording.

The cognitive task most commonly used to elicit event-related EEG activity is that of the active oddball paradigm (Donchin et al., 1973; O'connell et al., 2012; Polich & Kok, 1995). In this paradigm, a series of frequent (70%–80%) and rare (30%–20%) auditory or visual stimuli are presented to the participant. The participant must immediately respond to the rare (target) stimuli by button-press or other motor action, or by mental-counting the number of the stimuli (which are then reported to the experimenter at the end of the task) (Donchin et al., 1973; Horvath et al., 2018; O'connell et al., 2012; Polich & Kok, 1995). As compared to ERPs computed by averaging the EEG epochs related to frequent stimuli, ERPs for the target stimuli are characterized by a large parietal late positive potential peaking at ~300–400 ms post-stimulus, the so called P300 or P3b component, reflecting focused attention, decision making, and working memory (Donchin et al., 1973; O'connell et al., 2012; Polich & Kok, 1995).

Delayed latency and lower amplitude in the oddball P300 have repeatedly been observed in patients with AD at different clinical stages (Golob et al., 2007; Polich & Corey-Bloom, 2005). Effects have also been reported (though with less large-scale replication) for early sensory and sub-conscious attention components, such as the auditory steady-state, P50 and Mismatch Negativity (MMN), and later cognitive components, such as the N400, Late Positive Potential (LPP), P600 and Error Related Negativity (ERN) (Bobes et al., 2010; Olichney et al., 2002, 2006, 2011; Quiroz et al., 2011). Some of these early components have demonstrated translational equivalence to EEG work with rodents (Drinkenburg et al., 2015).

EEG activity recorded during cognitive tasks of episodic memory, language processing and executive function can provide further neurophysiological information in the frequency domain to enhance our understanding of the effects of AD on brain functions (Babiloni, Blinowska, et al., 2020). In this line, ERPs can be analyzed by decomposing the phase-locked EEG oscillatory impulses at delta, theta, alpha, beta, and gamma frequency bands that linearly compose them, the so-called event-related EEG oscillations (EROs; Herrmann & Knight, 2001; Lejko et al., 2020; Neuper et al., 2006; Yener & Başar, 2010; Yener & Başar, 2013).

The ongoing EEG activity recorded during cognitive tasks can also be linearly analyzed to exploit event-related increase or decrease in amplitude (power) of the ongoing oscillatory responses non-phase locked to the stimulus or response onset at delta, theta, alpha, beta, and gamma frequency bands, the so-called event-related desynchronization/synchronization (ERD/ERS) (Pfurtscheller and Lopes da Silva, 1999).

Such EROs and ERD/ERS measures have significant potential for understanding the abnormal cognitive neurophysiological systems that occur in AD relative to other dementias such as Parkinson's (PD), Lewy Body (LBD), and vascular cognitive impairment (VCI).

2 | AIMS AND METHODOLOGY

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), Alzheimer's Association (AA; https://www.alz.org/), formed a large Expert Panel to review the literature and provide recommendations on candidate ERO and ERD/ERS measures for characterizing neurophysiological oscillatory mechanisms in AD, PD, LBD, and VCI dementias. The Expert Panel was multidisciplinary and included expertize from the fields of neurology, psychiatry, and neuroimaging of dementias, clinical neurophysiology and quantitative EEG of dementias and cognitive and systems neurosciences. The Panel addressed the following specific question: What are the ERO and ERD/S measures that most consistently reveal abnormalities in brain neurophysiological oscillatory mechanisms in AD patients relative to age-matched cognitively unimpaired (CU) people and patients with PD, LBD, and cerebrovascular diseases?

To address to this question, the Panel pursued the following objectives: (1) identification of abnormal ERO and ERD/S measures in AD patients, (2) assessment of how these measures are affected by the progression of the cognitive impairment, and (3) the extent to which these measures can differentiate patient sub-groups.

A comprehensive literature search was completed on EROs and ERD/S in Alzheimer's disease patients with MCI (ADMCI) and dementia (ADD), Parkinson's disease patients with MCI (PDMCI) and dementia (PDD), LB disease with MCI (LBMCI), and dementia (LBD), and cerebrovascular disease with MCI and dementia (major and minor VCI).

The literature review was performed using the Scopus and PubMed databases, which were carefully searched by the authors (TA, EY, and BG) until November 4, 2020. Searches were performed under "Title, abstract and keywords" in Scopus, and "Title, abstract" in PubMed.

Keywords for the AD patients were as follows: "Dementia" OR "Mild Cognitive Impairment" AND "Brain Oscillation" OR "Event-Related Oscillation"; OR "Event-Related Desynchronization"; OR "Event-Related Synchronization"; OR "Induced Oscillation"; OR "Evoked Oscillation." Identical literature searches were carried out for patients with PD, LBD, and cerebrovascular disease with MCI and dementia (major and minor VCI).

All selected papers were critically reviewed by three members of the Expert Panel (BG, EY, and TA). Only event-related EEG studies were included. Studies using long stimuli (several hundreds of milliseconds) or where the analysis was not finely time-locked to the event onset, and those that used EEG measurements in patients in the resting state condition were excluded. Afterward, four members of the Expert Panel (BG, EY, TA, and CB) produced a first draft of the manuscript. This draft was sent to the co-Authors for amendments. Following revisions, the Panel reached a unanimous consensus about the findings and recommendations. The manuscript was finalized in mid-February and revised in July 2021.

It should be noted that the terms and methodological procedures discussed in this manuscript may *not* correspond to those used in daily medical practice, and we do not recommend that neurologists and psychiatrists use the present terms and procedures in their practice for diagnostic, prognostic, or monitoring purposes. Indeed, this manuscript is *not* a collection of guidelines for the application of techniques of clinical neurophysiology in daily medical practice. Similarly, the manuscript was not designed to suggest revisions to diagnostic criteria. Rather, it was designed to reach consensus recommendations on the optimal ERO and ERD/S measures to be used in clinical trials enrolling AD patients. Notably, the present review of the literature was not based on standard procedures typically adopted by international biomedical societies for the review of the medical intervention and practice (e.g., among them, see the *GRADE* Handbook to address the so-called *PICO* health care questions, https://gdt.gradepro.org/app/handbook/handbook.html). The authors hope that the field will soon reach maturity for involvement of international biomedical societies for that purpose.

Significant caveats and intrinsic limitations of this article include (i) the potentially restrictive criteria used for the literature review and classification; (ii) the inclusion of studies that have applied the heterogeneous diagnostic criteria for AD, which been used for decades, and therefore may not exclude AD patients with moderate cerebrovascular, non-AD hippocampal impairment (TDP-43), and Lewy body co-pathology, especially in older groups; (iii) the use of the term ADMCI to denote patients with amnesic MCI, thus suggesting possible prodromal ADMCI without a diagnosis based on in-vivo biomarkers of AD; (iv) the blurring effects of the head as a volume conductor spreading scalp EEG activity, and (v) heterogeneous procedures for the detection of artifacts in preliminary EEG data analysis.

3 | PROCEDURES FOR THE ANALYSIS OF EVENT-RELATED OSCILLATIONS (EROS) AND EVENT-RELATED DESYNCHRONIZATION/SYNCHRONIZATION (ERD/ERS)

In event-related EEG paradigms, many epochs (typically >20), each keyed to a time-locking stimulus or response event, are recorded in sequence to reach a sufficient signal-to-noise ratio. In any EEG epoch, event-related EEG potentials within ~1 s post-stimulus are embedded in greater non-phase locked ongoing EEG rhythms that are unrelated to the stimulus. After the averaging of all artifact-free EEG epochs related to the event onset, these potentials become visible in the ERPs and can be studied in terms of peak amplitude, latency, and topography (distribution over the scalp). Thanks to the averaging procedure, non-phase locked EEG rhythms unrelated to the event-onset are markedly reduced (Güntekin & Emek-Savaş, 2019; Luck, 2014).

Many measures can be derived from event-related EEG epochs as illustrated in Figure 1. In the following sections, we briefly review these and report main findings in understanding the pathophysiological oscillatory mechanisms generating abnormal EROs and ERD/ERS in patients with AD compared to other dementias.

3.1 | Event-related digital filtering of ERP

There is ongoing discussion about the optimal procedures to analyze and interpret scalp-recorded event-related EEG activity in time and frequency domains (Helfrich & Knight, 2019; Sauseng et al., 2007). From an analytical point of view, EEG activity can be decomposed as several overlapping oscillations of the voltage (i.e., waveforms), each characterized by: (i) a phase related to stimulus or response onset, (ii) a time evolution within 1s post-stimulus at frequency bands, and (iii) a scalp (source) topography of the maximum amplitude

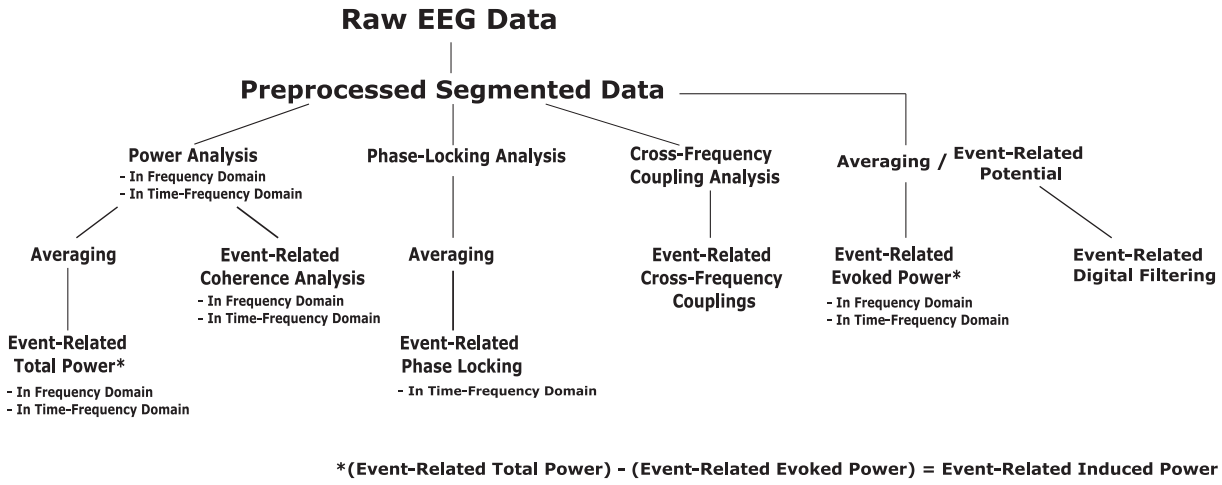

FIGURE 1 Common methodologies used in event-related oscillation studies

(Başar et al., 1992, 1999). Signal processing methods can be used to derive these oscillations from the original event-related EEG activity and analyze them separately (Başar, Gölbaşı, et al., 2016).

Decades ago, Erol Başar (1972) and colleagues proposed that averaged ERPs can be conceived as the superimposition of EEG oscillatory impulses (i.e., EROs), which are induced by sensory stimulus processing and be analyzed by spectral analysis techniques. Digital bandpass filtering is widely used to separate band frequency components forming ERPs such as delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (15–30 Hz), and gamma (28–48 Hz). The band passed ERPs at each frequency band (i.e., EROs) can be analyzed as peak-to-peak amplitude within 1s post-stimulus and topography (Güntekin & Emek-Savaş, 2019).

EROs can also be derived by the calculation of phase and power density from the averaged ERPs at frequency bands from delta to gamma (Başar, Gölbaşı, et al., 2016). In the analysis of EROs, the combination of results from digital filtering and power density analysis provides an enriched view of the underlying neurophysiological mechanisms generating event-related and phase-locked EEG activity (Başar, Gölbaşı, et al., 2016).

3.2 | Event-related power spectrum of EEG epochs

Spectral analysis can be applied on epochs at scalp electrodes or source estimates to derive other interesting measures of event-related EEG activity. This analysis can be performed by time-frequency procedures that take into account the intrinsic non-stationary nature of event-related EEG signals (Cohen, 2014; Güntekin & Emek-Savaş, 2019). Specifically, time-frequency analysis provides estimates of the power of event-related EEG epochs at frequency bands in relatively short time periods (~1 s post-stimulus). Short-time Fourier transform (STFT) and wavelet transform (WT) methods have gained in popularity for this purpose (Başar, Gölbaşı, et al., 2016).

The power of EEG activity in post-stimulus periods can be corrected for the pre-stimulus values as a type of "baseline correction". A popular procedure for baseline correction is ERD/S (Pfurtscheller & Andrew, 1999). For each EEG epoch, electrode, and frequency band of interest, ERD/S computes the time course of the percentage of power changes after a stimulus (or before the onset of a voluntary movement) relative to a previous period of background EEG activity. For any given period, a percentual decrease of EEG power at that frequency band (relative to baseline values) is called ERD, while a percentual increase is called ERS. Notably, this procedure investigates the event-related and non-phase-locked EEG oscillatory activity, so a model of ERPs is removed from any event-related EEG epoch before the computation of ERD/ERS (Pfurtscheller and Lopes da Silva, 1999).

Another methodological approach to investigate the time- and non-phase-locked component of event-related EEG activity is the computation of the so-called "induced" EEG power, as opposed to "evoked" EEG power computed applying spectral analysis on ERPs (Herrmann et al., 2004, 2014). The induced EEG power represents the time- and non-phase-locked component of event-related EEG activity. To compute this, EEG power is calculated by averaging the power of the single EEG epochs. Induced EEG power is then obtained by subtracting evoked power from total power (Herrmann et al., 2004, 2014).

3.3 | Event-related phase locking analysis of EEG epochs

Phase-locking analysis of event-related EEG activity at each electrode and frequency band of interest measures the consistency of the spectral phase values across all EEG epochs

related to single events. It is independent of EEG power computed in those epochs and reflects the stability in the phase-locking reactivity of underlying neurophysiological oscillatory mechanisms during the course of the experiment (Delorme & Makeig, 2004; Herrmann et al., 2004, 2014). Phase locking values are normalized between 0 and 1. For each electrode and frequency band of interest, a phase-locking value of 1 indicates that within the period of interest, the phase of the event-related EEG oscillatory impulse is equal across EEG epochs. In contrast, a phase-locking value of 0 represents random values of the phases of that oscillatory impulse across EEG epochs. A popular method to compute phase information is the Wavelet Transform, also termed as inter-trial coherence (Delorme & Makeig, 2004).

3.4 | Event-related coherence analysis of EEG epochs

Spectral coherence analysis of event-related EEG activity at a given frequency band measures the linear and bivariate interdependence of that activity at an electrode or source pair. This analysis is challenging due to issues of volume conduction, spatial blurring of EEG signals by the skull, and the indeterminacy of EEG source reconstruction techniques (Haufe et al., 2013; Mahjoory et al., 2017). Many other linear and non-linear procedures can be applied with the same purpose (Babiloni, Blinowska, et al., 2020). Caveats with the use of these techniques have recently been discussed by an International Federation of Clinical Neurophysiology Workgroup (Babiloni, Barry, et al., 2020). Simulated and empirical comparisons have shown sensor-based phase-lag approaches to be effective (Ruiz-Gómez et al., 2019).

3.5 | Event-related cross-frequency couplings of epochs

For each electrode, the cross-frequency coupling of event-related EEG activity measures the dependence of that activity at a frequency band on the activity computed at another frequency band. This analysis is based on previous evidence that EEG rhythms at low frequency bands (i.e., delta and theta) may trigger and frame operative EEG rhythms at higher frequency bands (i.e., beta and gamma; Canolty & Knight, 2010).

There are several different approaches to cross-frequency coupling analysis. Commonly used approaches include the computation of multiple coupled charateristics of event-related EEG activity, such as amplitude (of a frequency band)-amplitude (of another frequency band), power-power, phase-amplitude and phase-phase. Several mathematical methods can be used to test each cross-frequency coupling approach (Bruns et al., 2000; Canolty et al., 2006; Cohen, 2008, 2014; Friston, 1997; Martínez-Cancino et al., 2019; Penny et al., 2008; Tort et al., 2010; Voytek et al., 2013).

The event-related cross-frequency coupling analysis is used to evaluate the interdependence of the event-related EEG activity for an electrode (source) pair. In this analysis, the procedure computes the interrelatedness between a given spectral characteristic of the EEG activity at one electrode (source) with that computed at another electrode (source; Cohen, 2014). Therefore, it can be considered as an additional approach to the study of brain neural newtorks with EEG techniques.

4 | EVENT-RELATED OSCILLATION STUDIES IN ADMCI AND ADD PATIENTS

4.1 | Event-related delta responses in ADMCI and ADD patients

In wakefulness, scalp-recorded EEG oscillatory activity at delta frequencies occurs at ~0.5–3.5 Hz and may be generated mainly by cycles of hyperpolarization and depolarization in large populations of cortical pyramidal neurons via thalamic inputs (Steriade and Buzsaki, 1990; Steriade et al., 1990; Steriade, 1993). However, delta activity can also be recorded in several locations in the human brain, including the nucleus accumbens (Leung & Yim, 1993), ventral tegmental area (Grace, 1995), ventral pallidum (Lavin & Grace, 1996), and the brain stem (Lambertz & Langhorst, 1998).

Başar and Stampfer (1985) and Stampfer and Başar (1985) revealed the essential role of an event-related transient increase in EEG delta oscillations (i.e., hundreds of milliseconds) in CU adults during cognitive tasks including decision making and working memory. A similar transient increase in EEG delta responses was also found during the processing of emotional stimuli (Karamacoska et al., 2018; Maffei, 2020; Venturella et al., 2019). A typical experimental condition eliciting these delta oscillations is the "oddball" paradigm. In this task, widespread delta oscillations have been shown to increase in amplitude during rare auditory or visual "target" stimuli requiring a cognitive response, compared to frequent stimuli to be ignored (Bachman & Bernat, 2018; Basar & Stampfer, 1985; Demiralp et al., 2001; Güntekin & Başar, 2016; Stampfer & Başar, 1985). The topology of these delta responses varies according to stimulus modality. While visual and auditory oddball paradigms elicit higher frontal, central, and parietal delta responses, more complex visual stimuli with emotional contents elicit greater parietal and occipital delta responses (Güntekin & Başar, 2009, 2016; Güntekin et al., 2008; Venturella et al., 2019).

Evidence shows that physiological and pathological brain aging reduces the amplitude of event-related EEG delta responses (Emek-Savaş et al., 2016; Kurt et al., 2014; Michalopoulos et al., 2012; Schmiedt-Fehr and Başar-Eroğlu, 2011; Yener et al., 2013, 2014, 2016). For example, two studies by Emek-Savaş et al. (2016) and Schmiedt-Fehr and Başar-Eroğlu (2011) found lower delta responses to visual stimuli in older adults relative to younger adults during visual oddball and go/no-go tasks, respectively.

Similarly, Liu et al. (2012) analyzed event-related cross-mutual information between different electrodes in ADMCI patients, possibly due to AD, young adults, and CU older adults during auditory oddball paradigms. These authors reported reductions in event-related delta responses across multiple scalp regions in the older CU and ADMCI groups compared to the young group, and reductions in delta at parietal-occipital electrodes in ADMCI patients relative to CU groups (Liu et al., 2012). Furthermore, Michalopoulos et al. (2012) showed that progressive ADMCI patients had lower delta phase-locking compared to CU participants, but found no group differences in event-related delta power. Similarly, Başar's group showed that ADMCI patients had lower delta responses during auditory (Kurt et al., 2014) and visual oddball paradigms, compared to CU participants (Yener et al., 2013, 2014, 2016). Furthermore, Yener and Başar (2013) reported that delta responses to oddball target stimuli were less affected in ADMCI than ADD patients.

The effect of pathological brain aging on event-related EEG delta responses was even more pronounced in ADD patients. Yener et al. (2008), Yener et al. (2012) found marked decreases in topographically widespread delta EROs to auditory and visual oddball target stimuli in ADD patients compared to CU adults. Notably, delta responses of ADMCI patients and CU controls were positively correlated with frontal cortical gray matter volume (Yener et al., 2016). Similarly, event-related delta coherence over frontal-parietal electrode pairs was lower in ADD patients when compared to CU controls during the visual oddball paradigm (Başar et al., 2010; Güntekin et al., 2008). Caravaglios et al. (2008) and Tülay et al. (2020) confirmed the above effects, with some minor methodological differences.

As the successful processing of and reaction to oddball target stimuli requires selective attention and limited working memory load, it can be speculated that abnormal phase-locked delta EROs in ADMCI and ADD patients may reveal a dysfunction in those processes of executive function (Miyake et al., 2000). This dysfunction may be specific to the oddball, as Fraga et al. (2017) did not find any significant effect on delta EROs in ADMCI and ADD patients during the so-called N-back working memory task. In this task, the participant has must respond to the stimulus that appeared some (i.e., N) events before. As compared to the oddball paradigm, the N-back task imposes a larger load on working memory and cognitive control to mitigate interference effects. Thus, the relatively high background brain arousal occurring during the N-back task may reduce differences in phase-locked delta EROs between CU adults and ADD patients. Notably, a re-analysis of the same EEG datasets revealed that ADMCI patients had lower delta non-phase-locked ERD relative to CU persons. These results highlight the complex interrelatedness between parallel phase- and non-phase-locked neural synchronization mechanisms, brain arousal, stimulus information and cognitive-motor information processing.

Table 1 summarizes the studies on event-related delta responses in ADMCI and ADD patients in chronological order.

4.2 | Event-related delta responses in non-AD dementias

Caution is needed when considering reduced event-related delta responses as an electrophysiological biomarker for AD, as the effect may simply be a non-specific indicator of brain disorders.

Along this line, cognitively intact PD patients have shown lower delta EROs relative to CU adults during cognitive tasks (Emek Savaş et al., 2017), but not during emotional processing (Yuvaraj et al., 2016) or lateralization tasks (Schmiedt-Fehr et al., 2007). In a separate study, delta EROs during oddball target detection were lower as a function of cognitive decline in PD patients compared with CU participants (Güntekin et al., 2018), but no difference was found in delta evoked by auditory stimuli not associated with cognitive demands (Güntekin et al., 2018). In another study, Yener et al. (2019) compared event-related delta power and phase-locking responses during a visual oddball task between ADMCI, PDMCI, and CU groups. Results showed reduced event-related delta power in the PDMCI group compared to the CU group and reduced delta phase locking in the PDMCI group compared to the ADMCI group (Yener et al., 2019). Furthermore, Rosenblum et al. (2020) analyzed event-related power and phase-locking during visual and auditory oddball tasks in LBD and CU groups. Delta power responses were lower in the LBD than in the CU group during both visual and auditory versions of the task. In contrast, only delta phase-locking responses during the auditory oddball task were lower in the LBD than in the CU group (Rosenblum et al., 2020). These authors also showed that LBD patients' scores on the motor Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS- UPDRS) were negatively correlated with delta power responses to visual stimuli (Rosenblum et al., 2020).

Abnormalities in event-related delta responses have also been found in major VCI patients. Xu et al. (2011) reported reduced delta ERS during a visual oddball task in major VCI patients compared to CU controls over frontal, central, and

TABLE 1 Event-related delta responses in ADMCI and ADD patients

	Participants	Task	Frequency Delta	Results
Caravaglios et al. (2008)	• 21 Mild ADD • 16 CU	Auditory oddball task	Digital filtering (Single sweep maximum peak-to-peak amplitude)	Decreased response amplitude in ADD patients CU>ADD (particularly at frontal areas)
Yener et al. (2008)	• 11 Mild ADD (unmedicated) • 11 Mild ADD (medicated) • 20 CU	Visual oddball task	Digital filtering (maximum peak-to-peak amplitude)	Decreased Response Amplitude in ADD patients (for both ADD groups) CU>ADD (for the Cz and C3 locations) No medication effect on Delta
Güntekin et al. (2008)	• 10 Mild ADD (unmedicated) • 11 Mild ADD (medicated) • 19 CU	Visual oddball task	Event-related coherence	Decreased coherence in ADD patients (for both ADD groups): CU > unmedicated ADD (for the left fronto-parietal electrode pairs) CU > medicated ADD (for the right fronto-parietal electrode pairs) No medication effect on delta
Yener et al. (2009)	• 11 ADD (unmedicated) • 11 ADD (medicated) • 19 CU	Simple light task	Digital filtering (maximum peak-to-peak amplitude)	No difference
Başar et al. (2010)	• 19 Mild ADD (unmedicated) • 19 Mild ADD (medicated) • 19 CU	• Simple light task • Visual oddball task	• Event-related coherence • Sensory evoked coherence	Decreased event-related coherence in ADD patients (for both ADD groups) No difference in evoked coherence
Yener et al. (2012)	• 17 ADD (de-novo) • 17 ADD (medicated) • 17 CU	• Auditory oddball task • Simple auditory task	Digital filtering (maximum peak-to-peak amplitude)	Decreased response amplitude in ADD patients (for both ADD groups) No group difference during simple auditory task
Michalopoulos et al. (2012)	• 14 Progressive mild cognitive impairment (PMCI) • 12 CU	0-back task	Phase intertrial coherence Phase-shift Intertrial coherence Event-related synchronization, desynchronization ERD/ERS	Delta power: CU > PMCI
Yener et al. (2013)	• 18 ADMCI • 18 CU	Visual oddball paradigm	The maximum peak-to-peak amplitude	Delta response: CU > ADMCI for the fronto-central-parietal areas
Kurt et al. (2014)	• 22 ADMCI • 21 CU	Auditory oddball paradigm	The maximum peak-to-peak amplitude	Delta response: CU > ADMCI for the frontal and mid-centroparietal areas
Yener et al. (2014)	• 43 ADMCI • 41 CU	• Simple visual stimulation • Visual oddball paradigm	The maximum peak-to-peak amplitude	No difference for simple visual stimulation Delta response: CU > ADMCI, Females > males and gender difference was stronger in CU
Yener et al. (2016)	• 28 ADMCI • 28 CU	Visual oddball paradigm	The maximum peak-to-peak amplitude Volume of frontal cortex was estimated from MRIs	Delta response: CU > ADMCI The volume of the frontal cortex was positively correlated with frontal delta response for both CU and ADMCI groups

(Continues)

TABLE 1 (Continued)

	Participants	Task	Frequency Delta	Results
Fraga et al. (2017)	• 16 Mild ADD • 21 aMCI • 27 CU	n-back task	Event-related (de)synchronization (ERD/ERS)	No difference
Fraga et al. (2018)	• 15 Mild ADD • 21 ADMCI • 27 CU	n-back task	Event-related (de)synchronization (ERD/ERS)	Greater ERD response in ADD compared to CU particularly at temporal-parietal electrodes Greater ERD response in CU compared to the ADMCI particularly at centro-parietal electrodes
Yener et al. (2019)	• 30 ADMCI • 25 PD-MCI • 28 CU	Visual oddball paradigm	Event-related spectral perturbation Inter-trial coherence	Delta phase-locking: ADMCI > PD-MCI
Tülay et al. (2020)	• 33 ADD • 46 ADMCI • 48 CU	Visual oddball paradigm	Both evoked (phase-locked) and total (phase-locked + non-phase-locked) ERO powers	Delta total response: CU > ADMCI > ADD Delta evoked response: CU > ADD

Abbreviations: ADD, Alzheimer's disease dementia; ADMCI, Alzheimer's disease patients with mild cognitive impairment; aMCI, amnestic mild cognitive impairment; CU, cognitively unimpaired control; ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization.

parietal electrodes. Furthermore, Xu et al. (2015) reported a decrease in the pre- and post-stimulus interdependence of delta responses at electrode pairs in VCI patients. In similar experimental conditions, Lou et al. (2011) found reduced event-related delta synchronization in VCI patients, while Wang et al. (2016) identified an abnormal topology (i.e., clustering coefficient) in the event-related delta responses (graph-theory markers) in these patients, relative to controls (Wang et al., 2014, 2016).

Notably, the above abnormalities in event-related delta responses may not be specific to patients with dementia. Indeed, similar reductions in delta responses have been found in patients with schizophrenia (Bates et al., 2009; Doege, Jansen, et al., 2010; Doege, Kumar, et al., 2010; Ergen et al., 2008; Ford et al., 2008; Roschke and Fell, 1997) and bipolar disease (Atagün et al., 2014; Lundin et al., 2018). Moreover, patients with alcohol use disorder have been shown to exhibit lower event-related delta responses as compared to CU participants during go/no go (Kamarajan et al., 2004) and visual oddball tasks (Jones et al., 2006). Reduced event-related delta responses during the visual oddball tasks have also been observed in the adolescent children of parents with alcohol use disorder as compared to controls (Rangaswamy et al., 2007). Therefore, event-related delta responses during cognitive tasks may characterize impairments in brain disorders more broadly, rather than being a signature of AD or other dementias.

Table 2 summarizes the results of event-related oscillatory responses in all frequency bands in other types of ADMCI and dementia patients.

4.3 | Event-related theta responses in ADMCI and ADD patients

Similar to delta responses, previous studies have demonstrated transient event-related magnitude increases in EEG theta oscillations (i.e., hundreds of milliseconds) in CU participants during cognitive tasks. Studies also highlight lower event-related theta power in older relative to younger CU participants across various tasks. These include the Sternberg (Hogan et al., 2003), verbal working memory (Cummins & Finnigan, 2007), go/no-go (Schmiedt-Fehr and Başar-Eroglu, 2011), probabilistic learning (van de Vijver et al., 2014), Stroop (Tafuro et al., 2019), visual delayed match-to-sample, visual oddball (Kardos et al., 2014) and auditory oddball tasks (Müller et al., 2009). Similarly, the peak frequency of theta responses was lower in older adults (mean = 4.1 Hz) compared to the young adults (mean = 5.2 Hz; van de Vijver et al., 2014). Findings with other measures of event-related thetas responses, such as phase-locking and phase synchronization, were less robust (Aktürk et al., 2020; Kolev et al., 2009; Müller et al., 2009).

TABLE 2 Event-related oscillatory responses in patients with non-AD dementias

	Participants	Task	Methodology	Results
Babiloni et al. (2005)	• 10 Major VCI • 15 Mild ADD • 18 Young CU • 22 Older CU	Delayed response tasks (short-term memory and no memory load)	Power spectrum MEG analysis Individual alpha frequency (IAF) peak Event-related desynchronization (ERD)	*Alpha* The latency for the alpha ERD peak; DEM> Young CU; older CU > young CU The amplitude for the alpha ERD peak; DEM > young CU; DEM > older CU
Schmiedt-Fehr et al. (2007)	• 11 PD without cognitive deficits • 11 Age-matched CU • 11 Young CU	The Simon task	Peak-to-peak amplitude and latency analysis	*Delta* In PD patients, delayed delta responses Delta responses at occipital and parietal locations; PD patients > age-matched CU PD patients > young CU
Pugnetti et al. (2010)	• 21 PD • 7 PDD • 10 LBD • 14 CU	12-Hz intermittent photic stimulation	Global field synchronization (GFS)	*Alpha* In controls, increased GFS values during 12-Hz IPS Increase of alpha2 (11–13 Hz) GFS; CU > PD > LBD In PDD, no change
Lou et al. (2011)	• 12 Major VCI • 12 CU	The visual oddball paradigm	Multichannel linear descriptors analysis (which consist of three measures: Σ, Φ and Ω) Σ; global field power Φ; dominant frequency Ω; spatial complexity of the region; the synchronization between spatially distributed processes	*Delta, Theta* The synchronization between spatially distributed processes in the delta and theta frequency; major VCI > CU The global field power in the delta frequency; CU> major VCI The dominant frequency in the delta frequency; major VCI > CU MMSE scores were negatively correlated with the Ω and Φ values in the delta frequency In major VCI, decreased synchronization in the slow frequency band during target stimuli
Xu et al. (2011)	• 12 Major VCI • 12 Young CU • 12 Older CU	The visual oddball paradigm	Event-related synchronization (ERS) Event-related desynchronization (ERD)	*Delta* In VCI, lower delta ERS in comparison to CU in frontal, central and parietal regions In older CU, lower delta ERS compared with young CU only in central and parietal regions
Wang et al. (2014)	• 12 Major VCI • 12 CU	The visual oddball task	The short-window Directed Transfer Function (sDTF) connectivity analysis (to investigate the dynamic information flow)	*Alpha* In major VCI, decreased the dynamic information flow from parietal to frontal and central locations in delta, theta and lower alpha frequency band *Delta, Theta, and Alpha* The information flow from parietal to frontal and central locations in delta, theta and alpha frequency band; CU > major VCI

(Continues)

TABLE 2 (Continued)

	Participants	Task	Methodology	Results
Xu et al. (2015)	• 12 Early VCI • 12 CU	The visual oddball task	Directed transfer function (to estimate the information flow of brain activity) connectivity analysis for both pre-stim and post-stim Event-related spectral perturbation (ERSP) analysis	*Delta, Theta* In early VCI patients, decreased pre-stim interhemispheric connectivity in the delta and theta frequency In early VCI patients, decreased post-stim interhemispheric connectivity in the delta frequency band In early VCI patients, decreased post-stim parietal-to-frontal/ central connectivity in the delta frequency band In VCI patients, increased pre-stim from central to parietal in theta frequency band In VCI patients, increased post-stim connectivity in central locations in delta frequency
Wang et al. (2016)	• 18 Major VCI • 19 CU	The visual oddball task	Global field power analysis Directed transfer function causality connectivity analysis Network analysis	*Delta, Theta* In major VCI patients, lower outgoing information flow in the parietal region in delta frequency The clustering coefficient in delta, theta frequency band; CU> major VCI In major VCI patients, decreased out-degree and increased in-degree in the parietal location and decreased in-degree in the central location in delta frequency In major VCI patients, decreased out-degree and at parietal locations in theta frequency In major VCI, altered of the brain networks toward random networks *Alpha* The clustering coefficient alpha1 (8–10 Hz) frequency; CU> major VCI *Beta* In major VCI patients, decreased out-degree and increased in-degree at Pz site in beta frequency
Güntekin et al. (2018)	• 12 PD without cognitive deficits • 10 PDMCI • 10 PDD • 16 CU	• The simple auditory stimuli paradigm • The auditory oddball paradigm	Digitally filtered; The maximum peak to peak event-related delta responses	*Delta* In PD patients, decreased delta responses Event-related delta responses CU > PDD upon target stimulations CU highest delta responses; PDD lowest delta responses

(Continues)

TABLE 2 (Continued)

	Participants	Task	Methodology	Results
Yener et al. (2019)	• 30 Amnestic ADMCI • 25 PDMCI • 28 CU	The visual oddball paradigm	Event-related phase-locking analysis Event-related spectral perturbation analysis	*Delta, Theta, and Alpha* Delta power CU> PDMCI In PD-MCI, decreased delta, theta, and alpha phase-locking The decreased theta power in ADMCI and PDMCI More decreased theta power in PD-MCI PDMCI patients had lower alpha power than the CU and ADMCI
Rosenblum et al. (2020)	• 23 LBD • 22 CU	• The auditory oddball task • The visual oddball task	50−300 ms early sensory components 300−600 ms late cognitive components Event-related power and phase-locking analysis	*Delta, Theta* In LBD, decreased delta power for both visual and auditory tasks Delta power CU > LBD In LBD, lower delta phase locking for auditory task In LBD patients, decreased theta power for the visual task but not auditory task In LBD, lower theta phase locking for the visual task *Alpha, Beta* Increase of alpha power in LBD patients is higher than CU in later cognitive processing Increase of beta power in LBD patients is higher than CU in later cognitive processing
Güntekin et al. (2020)	• 15 PD without cognitive deficits • 22 PDMCI • 11 PDD • 17 CU	• The auditory oddball paradigm • The visual oddball paradigm	Event-related spectral perturbation analysis Event-related phase-locking analysis	*Theta* In CU, increased theta power and theta phase-locking Theta power and theta phase-locking CU> PDMCI; CU > PDD In PD patients, decreased theta responses

Abbreviations: ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization; DEM, dementia patients; PD, Parkinson's disease patients; PDMCI, Parkinson's disease patients with mild cognitive impairment; PDD, Parkinson's disease dementia; LBD, lewy body dementia; VCI, vascular cognitive impairment; CU, cognitively unimpaired control.

Concerning pathological brain aging, most studies showed a reduction of event-related theta power during memory tasks in ADMCI and ADD patients over CU participants. Karrasch et al. (2006) showed abnormal theta ERD (instead of ERS) in ADMCI patients during the short-term memory encoding phase of a Sternberg task, as well as an abnormal absence of theta ERS in ADD patients during the retrieval phase. Deiber et al. (2015) showed reduced event-related theta power and phase-locking in ADMCI patients relative to CU participants during a 2-back working memory task. Moreover, Cummins et al. (2008) found lower theta power during a modified Sternberg word recognition task in ADMCI patients compared to CU participants; ADMCI patients also showed lower theta power under high versus low memory load. In retrospective studies, ADMCI patients who converted to ADD (ADMCI converter) were found to have previously exhibited reduced event-related theta responses during an N-back task, relative to ADMCI non-converters and controls (Deiber et al., 2009, 2015; Missonnier et al., 2006). ADMCI converters were also characterized by lower event-related theta responses at the baseline recording session than at one-year follow-up (Deiber et al., 2009). Analogously, event-related theta responses during a word processing task were lower in ADMCI converters relative to CU participants and ADMCI non-converters (Mazaheri et al., 2018).

Similar effects were observed in non-memory cognitive tasks. Michalopoulos et al. (2012) found lower event-related theta power and theta phase-locking during a simple visual response task in ADMCI patients when compared to CU controls. Furthermore, Caravaglios et al. (2013) showed theta ERS lower in ADMCI patients relative to controls during temporal orienting of attention paradigm. Similarly, Yener et al. (2007) showed lower frontal theta phase-locking during a visual oddball task in non-medicated ADD patients as compared to CU participants. Tülay et al. (2020) also reported that event-related theta responses were lower in ADMCI and ADD patients relative to controls during a visual oddball task. In a separate study, Liu et al. (2012) showed that theta coherence at electrode pairs during an auditory oddball task was lower in ADMCI patients compared to CU participants. Finally, Güntekin et al. (2019) showed reduced event-related theta power during the recognition of facial expressions in ADD patients.

The impaired event-related theta responses in ADMCI and ADD patients may be strictly related to the pre-stimulus theta rhythms. Indeed, Caravaglios et al. (2010) and Goodman et al. (2019) reported greater pre-stimulus theta power and lower post-stimulus event-related theta responses in ADD patients when compared to CU adults.

Furthermore, these event-related theta responses may be sensitive to interventions for neuromodulation. Along this line, Mudar et al. (2019) showed that theta ERS during a go/no-go task increased in ADMCI patients as a function of cognitive training. Similarly, Cespón et al. (2019) investigated the effects of transcranial direct current stimulation (TDCs) over left dorsolateral prefrontal cortex in ADD patients and CU controls. The authors found that event-related theta responses (but not other frequency bands) during an N-back task were greater after the cathodal tDCS neuromodulation in ADD (but not controls) (Cespón et al., 2019). However, the impaired event-related dynamics were not unique for the theta responses in AD; therefore, more research is needed to find the right modulation for normalizing event-related delta, theta, alpha, beta, and gamma responses in these patients. In another study, Koch et al. (2018) studied the effect of non-invasive repetitive transcranial magnetic stimulations (rTMS) over the precuneus for two weeks on EEG activity evoked by a single pulse TMS on that cortical area in ADD patients. Results showed that rTMS intervention only modulated beta responses to the single pulseTMS (Koch et al., 2018).

In relation to the study of event-related theta power responses, other measures have shown mixed results in ADD patients, possibly due to the intrinsic features of spectral markers, task difficulty, and sample size differences. Sweeney-Reed et al. (2012) analyzed the event-related theta phase-locking in ADMCI patients and CU participants during a Deese-Roediger-MacDermott paradigm used to analyze neurophysiological mechanisms underlying false memory. In their study, ADMCI patients showed greater frontal theta event-related phase-locking as compared to CU participants (Sweeney-Reed et al., 2012). Furthermore, Yener and colleagues digitally filtered theta responses of ADMCI patients and controls during a visual oddball task and found no significant group differences (Yener et al., 2007, 2013). Later the same group showed that during simple visual stimulation, ADD patients without drugs had overexcited occipital regions that were represented with greater theta responses (Yener et al., 2009). Moreover, Fraga et al. (2017) found no significant effects on theta rhythms during the N-back visual task in ADD patients. Similarly, Kurimoto et al. (2012) reported no significant effects on theta rhythms during the Sternberg task when comparing ADD patients and CU participants. In a later study, Fraga et al. (2018) pointed to more theta ERD during an N-back task in ADMCI patients than ADD patients.

Table 3 summarizes the results of the event-related theta responses during cognitive tasks in ADMCI and ADD patients.

4.4 | Event-related theta responses in patients with non-AD dementias

Concerning non-AD dementias, the study of event-related theta responses have shown interesting findings. Yener et al. (2019) showed that event-related theta power during a

TABLE 3 Event-related theta responses in ADMCI and ADD patients

	Participants	Task	Frequency theta	Results
Karrasch et al. (2006)	• 7 ADD • 7 Mild ADMCI • 10 CU	Auditory-verbal Sternberg's memory search paradigm	Event-related desynchronization (ERD) and synchronization (ERS)	The responses in the 5–7 Hz; Increased ERD in ADMCI, Increased ERS in the CU and AD During retrieval: The responses in the 4–5 Hz; Increased ERS in the ADMCI but not in the ADD There was no significant difference between ADD and controls in the low theta band (3–6 Hz)
Missonnier et al. (2006)	• 24 ADMCI At 1-year follow-up • 13 Progressive ADMCI • 11 Stable ADMCI	n-back working memory task	Event-related synchronization (ERS)	Theta ERS power: Stable ADMCI > Progressive ADMCI
Yener et al. (2007)	• 11 ADD (unmedicated) • 11 ADD (medicated) • 20 CU	Visual oddball	Phase-locking analysis	Decreased phase locking in Untreated ADD patients at F3 location Increased phase locking in treated ADD patients at F3 location untreated ADD < treated ADD, CU
Güntekin et al. (2008)	• 10 Mild ADD (unmedicated) • 11 Mild ADD (medicated) • 19 CU	Visual oddball	Event-related coherence	Decreased coherence in ADD patients (for both ADD group): CU > unmedicated ADD, medicated ADD (for the left fronto-parietal electrode pairs) No medication effect on theta
Cummins et al. (2008)	• 12 ADMCI • 12 CU	The modified Sternberg word recognition task	Spectral power	Theta power: During the retention; CU > ADMCI at the Pz and T7 electrodes During the recognition; CU > ADMCI at the C3 and F3 electrodes In ADMCI patients, theta power decreased with increasing memory load
Yener et al. (2009)	• 11 ADD (unmedicated) • 11 ADD (medicated) • 19 CU	Simple light task	Digital filtering (maximum peak-to-peak amplitude)	Increased response in unmedicated ADD patients
Deiber et al. (2009)	• 29 ADMCI • 24 CU At 1-year follow-up • 16 Progressive ADMCI • 13 Stable ADMCI	n-back working memory task	Event-related global theta oscillatory activity Event-related induced theta oscillatory activity	At 1-year follow-up; Induced theta activity at baseline: progressive ADMCI < CU, stable ADMCI
Başar et al., 2010	• 19 mild ADD (unmedicated) • 19 mild ADD (medicated) • 19 CU	• Simple Light task • Visual Oddball task	• Event-Related Coherence • Sensory evoked coherence	Decreased Event-Related Coherence in ADD patients (for both ADD group) No difference in Evoked Coherences
Caravaglios et al. (2010)	• 22 Mild ADD • 16 CU	Auditory oddball	Event-related power	Increased pre-stimulus power in ADD patients No post stimulus enhancement in ADD compared to pre-stimulus

(Continues)

TABLE 3 (Continued)

	Participants	Task	Frequency theta	Results
Kurimoto et al. (2012)	• 13 ADD • 13 ADMCI • 14 CU	Modified version of Sternberg's task	Event-related (de)synchronization (ERD/ERS)	No difference
Liu et al. (2012)	• 16 ADMCI • 15 Older CU • 16 Young CU	Auditory oddball	Cross-mutual information analysis (measures the corticocortical connections)	Significant difference between older CU and ADMCI (except in the occipital lobe)
Sweeney-Reed et al. (2012)	• 9 ADMCI • 11 CU	The DRM paradigm (examining false memories)	Phase synchrony (functional connectivity) amplitude	Theta phase-locking: ADMCI > CU at the frontal areas Lower fronto-parietal interaction in the ADMCI No difference in amplitude
Michalopoulos et al. (2012)	• 14 Progressive ADMCI • 12 CU	0-Back task	Phase inter-trial coherence Phase-shift Inter-trial coherence Event-related synchronization, desynchronization ERD/ERS	Induced theta activity: lower in the progressive ADMCI Theta power: Progressive ADMCI < CU
Yener et al. (2013)	• 18 ADMCI • 18 CU	Visual oddball paradigm	The maximum peak-to-peak amplitude	Theta oscillatory responses had no group difference
Caravaglios et al. (2013)	• 25 ADMCI • 15 CU	The temporal orienting of attention paradigm	Event-related synchronization/desynchronization (ERS/ERD)	Pre-event theta ERS: CU > ADMCI at temporal electrodes Post-motor theta ERS: CU > ADMCI at prefrontal areas CU showed lateralization effect: pre-event theta ERS pronounced on the right posterior temporal locations while the post-motor theta ERS mostly pronounced on the left, as well as the midline prefrontal areas
Deiber et al. (2015)	• 45 ADMCI • 97 CU Upon 18-month neuropsychological follow-up: • 55 stable (sCON) • 42 deteriorated (dCON)	• Simple attentional task • 2-Back working memory task	ERD/ERS: event-related desynchronization/synchronization, ITC: inter-trial coherence	Theta ITC: ADMCI < dCON, sCON Theta ERS: ADMCI< sCON
Fraga et al. (2017)	• 16 Mild ADD • 21 ADMCI • 27 CU	n-back task	Event-related (de)synchronization (ERD/ERS)	No difference
Fraga et al. (2018)	• 15 mild ADD • 21 ADMCI • 27 CU	n-back task	Event-related (de)synchronization (ERD/ERS)	Greater ERD response in ADD compared to CU Greater ERD response in ADMCI compared to ADD No difference in ADMCI-CU comparison

(Continues)

TABLE 3 (Continued)

	Participants	Task	Frequency theta	Results
del Val et al. (2018)	• 34 ADMCI • 16 ApoE ε4 carriers (ε4+) ADMCI • 18 ApoE ε4 noncarriers (ε4−) ADMCI • 26 CU	Associative memory • The biographical matching task (congruent/ incongruent famous faces and non-famous faces) • Conceptual priming task • Visuospatial memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Volumetric measures were obtained for left and right sides of the hippocampus and the intracranial volume	Theta ERS: CU > ADMCI ApoE ε4 + CU > ADMCI ApoE ε4−
Mazaheri et al. (2018)	• 15 ADMCI convertors group: Developed ADD within 3-years • 10 ADMCI non-convertors group • 11 CU	Word comprehension task: Congruent or incongruent category	Time-frequency representations (TFRs) of power Cross-frequency coupling between theta and alpha/beta	Theta activity (3–5 Hz): During a word processing task; ADMCI convertors < CU, ADMCI non-converters Increased central theta associated with word congruency: ADMCI convertors < CU, ADMCI non-converters
Koch et al. (2018)	14 Early ADD	Transcranial magnetic stimulation (TMS)-evoked	• Event-related spectral perturbation / Event-related power analysis • Inter-trial coherence /Event-related phase locking analysis	No difference
Goodman et al. (2018)	• 33 ADD • 34 ADMCI • 31 CU	n-back task	Event-related theta-gamma coupling	Lowest theta-gamma coupling in ADD (on 2-back task): ADD<ADMCI<CU
Goodman et al. (2019)	• 29 ADD • 100 ADMCI • 40 CU	n-back task	Ratio of post stimulus power to pre stimulus power	Small theta ratio in ADD compared to CU (on 2-back task)
Yener et al. (2019)	• 30 ADMCI • 25 PD-MCI • 28 CU	Visual oddball paradigm	Event-related spectral perturbation Inter-trial coherence	Theta power: PD-MCI and ADMCI < CU (more prominent in PD-MCI than ADMCI) Theta phase-locking: PD-MCI < ADMCI and CU
Mudar et al. (2019)	32 ADMCI Participants completed the two cognitive training programs: 16 Gist reasoning 16 New learning	Go/NoGo tasks	Event-related power	Greater theta ERS at parietal locations post-training than pre-training

(Continues)

TABLE 3 (Continued)

	Participants	Task	Frequency theta	Results
Güntekin et al. (2019)	• 30 ADD • 30 CU	Facial expression	• Event-related power • Event-related phase locking	Decreased event-related power in ADD patients (during the angry facial expression) No group difference in theta phase locking
Cespon et al. (2019)	• 14 ADD • 12 CU	n-back task	Event-related power analysis	After cathodal tDCS: Greater Theta Power in ADD patients No difference in CU after tDCS compared the before
Serrano et al. (2020)	• 45 ADMCI • 49 SCD (Subjective cognitive decline) • 49 CU	Working memory task	Time-frequency analysis Event-related power	Theta power CU > ADMCI SCD > ADMCI
Tülay et al. (2020)	• 33 ADD • 46 ADMCI • 48 CU	Visual oddball paradigm	Both evoked (phase-locked) and total (phase-locked + non-phase-locked) ERO powers	Theta total response: ADD < ADMCI < CU

Abbreviations: ADD, Alzheimer's disease dementia; ADMCI, Alzheimer's disease patients with mild cognitive impairment; CU, cognitively unimpaired control; ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization; tDCS, transcranial direct current stimulation.

visual oddball task was lower in both ADMCI and PDMCI patients compared to CU adults. Furthermore, theta phase-locking was lower in PDMCI but not ADMCI patients when compared to controls (Yener et al., 2019). Rosenblum et al. (2020) showed that event-related theta power and phase-locking during a visual (but not auditory) oddball task was lower in LBD patients than in CU participants. Yener et al. (2019) reported that event-related theta power during a visual oddball task was lower in PDMCI than in ADMCI patients and lower in all patients than in CU participants. Furthermore, theta phase-locking was lower in PDMCI (but not ADMCI) than in CU participants (Yener et al., 2019). Similarly, Güntekin et al. (2020) reported that event-related theta power and phase locking during a visual and auditory oddball tasks were lower in PDD than PDMCI patients and lower in PDMCI patients than PD patients without cognitive deficits and controls.

Concerning cerebrovascular disease, Xu et al. (2015) reported that event-related measures of interdependence of theta rhythms at parieto-occipital electrode pairs during a visual oddball paradigm were lower in major VCI patients as compared to CU adults. Furthermore, the topology of the interdependence as indexed by graph theory markers showed a lower clustering coefficient in the theta band as compared to CU controls (Wang et al., 2014, 2016).

Table 2 summarizes the results for the event-related theta responses during cognitive tasks in patients with non-AD dementias. In general, event-related delta and theta power, phase-locking, and coherence during cognitive tasks were increased in CU participants (Başar et al., 2001; Cavanagh & Frank, 2014; Cohen & Cavanagh, 2011; Gevins et al., 1997; Gruber et al., 2018; Hsieh & Ranganath, 2014; Jensen & Tesche, 2002; Klimesch, 1999; Sauseng et al., 2010). Furthermore, some markers of event-related theta responses (particularly event-related power) were lower in ADMCI and ADD patients compared to CU adults (Başar et al., 2010; Caravaglios et al., 2010; Güntekin et al., 2008; Tülay et al., 2020; Yener et al., 2007). However, these effects may be non-specific as similar changes were observed in PDMCI (Güntekin et al., 2020; Yener et al., 2019), PDD (Güntekin et al., 2020), LBD (Rosenblum et al., 2020), and major VCI patients (Lou et al., 2011; Wang et al., 2016; Xu et al., 2011, 2015). Future comprehensive EEG experiments are therefore needed to compare event-related delta and theta responses among patients with different dementias at different levels of cognitive deficits.

4.5 | Event-related alpha responses in ADMCI and ADD patients

Since the first discovery of EEG recordings (Berger, 1929), alpha rhythms (8–13 Hz) have been considered as the

dominant posterior oscillatory cortical activity observed in adults resting in quiet vigilance (Babiloni, Barry, et al., 2020). During development, the alpha frequency peak is observed at 5–10 Hz in infants and at 9–11 Hz in adolescents (Marcuse et al., 2008; Stroganova et al., 1999). During later life, alpha rhythms show lower amplitude and slower frequency peak (Babiloni et al., 2006; Hashemi et al., 2016; Ishii et al., 2017; Klass and Brenner, 1995; Klimesch, 1999). These effects are even more pronounced during pathological brain aging in dementia (Babiloni et al., 2004; Babiloni, Frisoni, et al., 2009; Babiloni, Ferri, et al., 2009; Babiloni, Pascarelli, et al., 2020; Dunkin et al., 1994; Leuchter et al., 1987; Locatelli et al., 1998; Rossini et al., 2007; Rossini et al., 2020).

Previous studies have shown mixed effects of aging on event-related alpha responses. On the one hand, several studies reported greater event-related alpha phase locking (Kolev et al., 2002; Yordanova et al., 1998) and power density (Aktürk et al., 2020; Babiloni et al., 2004; Karrasch et al., 2004; Schmiedt-Fehr et al., 2016; Strunk et al., 2017) during auditory and visual tasks in older compared to younger CU adults. Furthermore, Dushanova and Christov (2014) showed that stimulus-evoked alpha responses were greater in older compared to younger CU adults, while the opposite was true for event-related alpha responses during cognitive demands. Moreover, other studies have reported delayed event-related alpha responses in older relative to younger CU adults (Deiber et al., 2010; Nguyen et al., 2020; Zanto et al., 2010). On the other hand, several studies found no significant aging effects on event-related alpha responses raising the issue of reliability of such measures (Kober et al., 2016; Mishra et al., 2013; Schmiedt-Fehr et al., 2009).

Similarly, previous studies have yielded mixed findings regarding event-related alpha responses in ADMCI patients. On the one hand, some studies reported significant effects. For example, Karrasch et al. (2006) showed alpha ERS during a Sternberg short-term memory paradigm in CU participants but not ADMCI patients. Furthermore, Mazaheri et al. (2018) reported that the alpha ERD during a word processing task diminished during each repetition of the words in CU participants but not ADMCI patients. Caravaglios et al. (2015) also found that post-stimulus alpha ERS during an attention task was lower in ADMCI patients than in CU participants. Along the same line, Deiber et al. (2015) showed that event-related alpha phase-locking during a 2-back working memory task was lower in ADMCI patients compared to controls. In contrast, Yener et al. (2019) found no differences in event-related alpha responses during a visual oddball paradigm between ADMCI and CU groups. Tülay et al. (2020) also found no difference in event-related alpha responses during a visual oddball paradigm among groups of ADMCI, ADD, and CU participants.

Concerning disease prediction, Michalopoulos et al. (2012) reported that event-related alpha power and phase-locking during a 0-back task were lower in ADMCI patients progressing to dementia over those who were clinically stable. Similarly, Del Val et al. (2016) showed that alpha ERD during a face memory task was lower in the former than the latter group.

Previous studies have also produced mixed findings on event-related alpha responses in ADD patients. Specifically, Güntekin et al. (2019) showed that event-related alpha responses (right hemisphere) during the detection of facial expressions was lower in ADD patients than in CU controls. Along the same line, Karrasch et al. (2006) showed lower ERD alpha responses during an auditory-verbal Sternberg task in ADD patients relative to CU controls. Similar effects were also observed by Fraga et al. (2017) during an N-back task. On the contrary, Babiloni et al. (2005) reported that alpha ERD responses during a short-term memory task were greater and temporally delayed in ADD patients relative to CU participants. Furthermore, several studies found no differences in event-related alpha responses during cognitive tasks between ADD and CU groups (Cespon et al., 2019; Goodman et al., 2019; Güntekin et al., 2019; Koch et al., 2018; Tülay et al., 2020; Yener et al., 2009).

Table 4 reports the above findings.

4.6 | Event-related alpha responses in patients with non-AD dementias

Findings regarding event-related alpha responses in patients with dementia not due to AD have also been mixed.

Concerning brain diseases due to α-synucleopathy, Yener et al. (2019) showed that event-related alpha power and alpha phase-locking during a visual oddball paradigm were lower in PDMCI patients relative to ADMCI patients and CU controls. Furthermore, Pugnetti et al. (2010) reported alpha responses during 12-Hz intermittent photic stimulations in CU participants but not in PDD patients. Finally, Rosenblum et al. (2020) showed that alpha responses in the 300–700 ms post-stimulus were reduced in LBD patients relative to CU controls during visual and auditory oddball paradigms.

Abnormal event-related alpha responses have also been observed in VCI patients, though the methodological approaches and findings have been varied. In one study, Babiloni et al. (2005) showed that, like ADD patients, major VCI patients had greater and delayed alpha ERD responses during a short-term memory task when compared with CU controls. In two separate studies, Wang et al. (2014, 2016) showed that major VCI patients were characterized by a lower clustering coefficient in the event-related alpha responses recorded during a visual oddball task, relative to controls,. Notably, Wang et al. (2016) analyzed the event-related responses with graph theory methodology and showed abnormal alpha responses in major VCI patients compared to controls.

TABLE 4 Event-related alpha responses in ADMCI and ADD patients

	Participants	Task	Frequency alpha	Results
Babiloni et al. (2000)	• 13 ADD • 13 Young CU • 13 older CU	Movement-related	Event-related (de)synchronization (ERD/ERS)	Greater "post-movement" contralateral alpha ERS in CU compared to ADD
Babiloni et al. (2005)	• 10 VCI • 15 Mild ADD • 18 young CU • 22 Older CU	Delayed response tasks (short-term memory (STM) and no memory load (no STM))	Power spectrum MEG analysis Individual alpha frequency (IAF) peak Event-related desynchronization (ERD)	The latency of the alpha ERD peak DEM> young CU, older CU >Young The amplitude of the alpha ERD peak DEM > young CU DEM > older CU
Karrasch et al. (2006)	• 7 ADMCI • 7 ADD • 10 CU	Auditory-verbal Sternberg's memory search paradigm	ERD/ERS responses analyzed both for the encoding and retrieval	During encoding: The responses in the 10–20 Hz; Increased ERS in the CU and Increased ERD in the ADMCI The responses in the 12–14 Hz; Increased ERD in the ADMCI, but not in the ADD
Güntekin et al. (2008)	• 10 Mild ADD (unmedicated) • 11 Mild ADD (medicated) • 19 CU	Visual oddball	Event-related coherence	CU > unmedicated ADD (for the left fronto-parietal electrode pairs) medicated ADD > unmedicated ADD (for the left fronto-parietal electrode pairs)
Yener et al. (2009)	• 11 ADD (unmedicated) • 11 ADD (medicated) • 19 CU	Simple light task	Digital filtering (maximum peak-to-peak amplitude)	No difference
Başar et al. (2010)	• 19 Mild ADD (unmedicated) • 19 Mild ADD (medicated) • 19 CU	Visual oddball task Simple light task	Event-related coherence Sensory evoked coherence	Decrease in the event-related coherence in ADD patients No difference for evoked coherence
Deiber et al. (2010)	• 43 ADMCI • 16 sd-ADMCI (single-domain ADMCI) • 27 md-ADMCI (multi-domain ADMCI) • 36 CU	Delayed match-to-sample tasks for face and letter stimuli	Event-related (de)synchronization (ERD/ERS)	Alpha ERS: During encoding; md-ADMCI < sd-ADMCI < CU
Michalopoulos et al. (2012)	• 14 Progressive ADMCI • 12 CU	0-back task	Phase Inter-trial Coherence Phase-shift Inter-trial coherence Event-Related Synchronization, desynchronization ERD/ERS	Alpha power and phase-locking: Progressive ADMCI < CU ERD of alpha induced response prolonged in Progressive ADMCI compared to CU
Sweeney-Reed et al. (2012)	• 9 ADMCI • 11 CU	The DRM paradigm (examining false memories)	Phase synchrony (functional connectivity) Amplitude	Reduced fronto-parietal interaction in the ADMCI No difference in amplitude
Kurimoto et al. (2012)	• 13 ADD • 13 ADMCI • 14 CU	Modified version of Sternberg's task	Event-related (de)synchronization (ERD/ERS)	No difference

(Continues)

TABLE 4 (Continued)

	Participants	Task	Frequency alpha	Results
Yener et al. (2013)	• 18 ADMCI • 18 CU	Visual oddball paradigm	The maximum peak-to-peak amplitude	There were no statistical differences across the groups for alpha responses
Caravaglios et al. (2015)	• 27 ADMCI patients • 15 CU	The temporal orientation of attention paradigm	Event-related synchronization/desynchronization (ERS/ERD)	Pre-event upper-alpha ERD: CU > ADMCI at the temporal and posterior areas Post-event upper-alpha ERS: ADMCI < CU at prefrontal areas
Deiber et al. (2015)	• 45 ADMCI • 97 CU persons Upon 18-month neuropsychological follow-up: • 55 stable (sCON) • 42 deteriorated (dCON)	Simple attentional task 2-back working memory task	ERD/ERS: event-related desynchronization/synchronization, ITC: inter-trial coherence	Alpha ITC: ADMCI < dCON, sCON Alpha ERD: dCON > sCON
Prieto del Val et al. (2015)	• 34 ADMCI • 16 ApoE ε4 carriers (ε4+) ADMCI • 18 ApoE ε4 noncarriers (ε4−) ADMCI • 26 CU	Associative memory The biographical matching task (congruent/incongruent famous faces and nonfamous faces) Conceptual priming task Visuospatial memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Cortical source imaging	High alpha ERD: CU > ADMCI CU > ADMCI ApoE ε4+ at the frontal sources CU > ADMCI ApoE ε4− at frontal and temporal sources
del Val et al. (2016)	• 16 ADMCI-c: ADMCI individuals that, within a 2-year follow-up period, developed dementia • 18 ADMCI-s: Stable ADMCI • 26 CU	Famous or non-famous faces: Encoding task Conceptual priming task Memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Volumetric measures were obtained for left and right sides of the hippocampus and amygdala	Alpha ERD: During memory Recognition; ADMCI-s>ADMCI-c During both encoding and memory task; ADMCI-c<ADMCI-s
Fraga et al. (2017)	• 16 mild ADD • 21 Amnestic ADMCI • 27 CU	n-back task	Event-related (de)synchronization (ERD/ERS)	Lower ERD response in ADD and ADMCI compared to CU
Fraga et al., 2018	• 15 mild ADD • 21 ADMCI • 27 CU	*n*-back task	Event-related (de)synchronization (ERD/ERS)	Alpha ERD; CU>ADD Alpha ERD; CU>ADMCI No difference in ADMCI-ADD comparison

(Continues)

TABLE 4 (Continued)

	Participants	Task	Frequency alpha	Results
Koch et al. (2018)	14 early ADD	Transcranial magnetic stimulation (TMS)-evoked	Event-related spectral perturbation / Event-related power analysis Inter-trial coherence /Event-related phase locking analysis	No difference
del Val et al. (2018)	• 34 ADMCI • 16 ApoE ε4 carriers (ε4+) ADMCI • 18 ApoE ε4 noncarriers (ε4−) ADMCI • 26 CU	Associative memory The biographical matching task (congruent/ incongruent famous faces and non-famous faces) Conceptual priming task Visuospatial memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Volumetric measures were obtained for left and right sides of the hippocampus and the intracranial volume	Alpha ERD: ADMCI ApoE ε4−>ADMCI ApoE ε4+
Mazaheri et al. (2018)	• 15 ADMCI convertors group: Developed ADD within 3-years • 10 ADMCI non-convertors group • 11 CU	Word comprehension task: Congruent or incongruent Category	Time-frequency representations (TFRs) of power Cross-frequency coupling between theta and alpha/beta	Late alpha (9–11 Hz) suppression: diminished with each repetition of the word in the CU but not in the both ADMCI group
Fodor et al. (2018)	• 17 ADMCI • 21 CU	Sternberg working memory task	Event-related spectral perturbation	Alpha ERS: ADMCI<CU persons during retention
Yener et al. (2019)	• 30 ADMCI • 25 PDMCI • 28 CU	Visual oddball paradigm	Event-related spectral perturbation Inter-trial coherence	Alpha phase-locking: PDMCI<CU and ADMCI
Mudar et al. (2019)	• 32 ADMCI Participants completed two cognitive training programs: • 16 Gist Reasoning • 16 New Learning	Go/No Go tasks	Event-related power	During response inhibition: Greater low and high frequency alpha ERD pre-training than post-training at frontal locations During response execution: Greater high-frequency alpha ERD post-training than pre-training at the frontal locations
Goodman et al., 2019	• 29 ADD • 100 ADMCI • 40 CU	n-back task	Ratio of post stimulus power to pre stimulus power	No difference
Güntekin et al. (2019)	• 30 ADD • 30 CU	Facial expression	Event-related power Event-related phase locking	Decreased right hemisphere event-related power in ADD patients No group difference in alpha phase locking

(Continues)

TABLE 4 (Continued)

	Participants	Task	Frequency alpha	Results
Cespon et al. (2019)	• 14 ADD • 12 CU	n-back task	Event-related power analysis	No significant difference
Serrano et al. (2020)	• 45 ADMCI • 49 SCD (Subjective cognitive decline) • 49 CU	Working memory task	Time-frequency analysis Event-related power	Alpha power CU > ADMCI SCD > ADMCI
Tülay et al. (2020)	• 33 ADD • 46 ADMCI • 48 CU	Visual oddball paradigm	Both evoked (phase-locked) and total (phase-locked + non-phase-locked) ERO powers	No statistical differences across the groups for alpha responses

Abbreviations: ADMCI, Alzheimer's disease patients with mild cognitive impairment; ADD, Alzheimer's disease dementia; CU, cognitively unimpaired control; DEM, dementia patients; ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization.

4.7 | Event-related beta responses in ADMCI and ADD patients

Multiple studies showed a strong relationship between cortical beta rhythms and voluntary movements in humans (Engel & Fries, 2010; Neuper et al., 2009; Pfurtscheller et al., 1996). Changes in cortical beta rhythms were also related to increased attention, working memory, emotional arousal, and other cognitive processes (Engel & Fries, 2010; Güntekin and Basar, 2007, 2010; Güntekin et al., 2013; Wróbel, 2000). Evidence also suggests that event-related beta responses during cognitive tasks may change across the lifespan. Wiesmann and Wilson (2019) reported that beta responses during a visuospatial discrimination task were negatively correlated with age, particularly over the somatomotor area. Furthermore, Wang et al. (2017) showed greater interrelatedness of beta rhythms during an audiovisual task in older relative to younger CU individuals.

Findings regarding event-related beta responses in ADMCI and ADD patients have been mixed. On the one hand, beta responses during cognitive tasks increased with cognitive load in CU participants but not ADMCI patients (Deiber et al., 2015; Güntekin et al., 2013; Missonnier et al., 2007). For example, Missonier et al. (2007) investigated event-related beta responses during an N-back task in ADMCI, ADD, and CU groups. Results showed that ADMCI patients who later progressed to dementia had lower beta responses compared to CU and stable ADMCI groups. Furthermore, Güntekin et al. (2013) reported that CU participants (but not ADMCI patients) exhibited higher beta responses during oddball targets in comparison to non-target stimuli. In the same vein, Deiber et al. (2015) showed lower beta phase locking during a 2-back working memory task in ADMCI patients relative to cognitively stable CU participants.

On the other hand, Caravaglios et al. (2018) presented greater beta phase locking in ADMCI patients compared to CU participants during a task using omitted stimuli. In the same study, beta power was found to be lower in the ADMCI group than in CU group. Furthermore, del Val et al. (2016) showed lower ERD during a memory task in ADMCI patients relative to CU participants. Fraga et al. (2017) reported the same effect during an N-back task. In contrast, Mazaheri et al. (2018) found increased beta ERD in ADMCI patients relative to CU participants during a word comprehension task. Furthermore, Tülay et al. (2020) found no differences in total and evoked beta power between ADMCI and CU groups during a visual oddball task.

Mixed results were also reported for event-related beta responses even in studies focused on ADD patients. Specifically, Missonnier et al. (2007) reported that beta ERS were similarly lower in ADMCI patients (who progressed to dementia) and ADD patients than in CU participants during an N-back task. Furthermore, there were no differences

between ADMCI patients who progressed to dementia and ADD patients (Missonnier et al., 2007). Along the same line, Fraga et al. (2017) reported lower beta ERD for both ADMCI and ADD patients during the N-back task, as compared to CU controls.

In contrast, Babiloni et al. (2000) showed greater beta ERD during voluntary movements and lower post-movement beta ERS in ADD patients relative to CU controls. Similarly, Koch et al. (2018) reported that repetitive TMS (rTMS) over the precuneus induced greater beta power and phase-locking in ADD patients than in controls. In addition, several studies found no difference in event-related beta responses between ADD patients and controls. For example, no beta differences were reported by Yener et al. (2009) using a simple sensory visual task (digital filtering of ERP responses), Tülay et al. (2020) using a visual oddball task (total and evoked power), Başar et al. (2010) using visual sensory and oddball tasks (event-related coherence analysis) or Cespon et al. (2019) using an N-back task. Table 5 summarizes the results of event-related beta responses in ADMCI and ADD patients.

4.8 | Event-related beta responses in patients with non-AD dementias

Mixed results have also been reported for event-related beta responses in patients with MCI and dementia not due to AD. In one study, Rosenblum et al. (2020) showed an increase of beta power during auditory and visual oddball paradigms in LBD patients as compared to CU controls. Using graph theory, Wang et al. (2016) showed abnormal indexes in major VCI patients compared to controls at delta, theta, alpha, and beta frequency bands. In relation to the CU group, major VCI patients were characterized by a lower graph clustering coefficient at the beta and other bands (Wang et al., 2016).

Keeping in mind the above results, event-related beta responses may be abnormal in AD, LBD, and VCI patients, but further studies are needed to define optimal experimental conditions to obtain repeatable and clinically significant results.

4.9 | Event-related gamma responses in ADMCI and ADD patients

Gamma responses have been associated with multiple functional roles, similar to the other frequency bands. Earlier studies showed the role of event-related gamma responses in sensory information processing in hedgehogs (Adrian, 1942), rabbits (Freeman, 1975), and cats (Başar et al., 1975), while Gray and Singer (1989) defined the role of gamma responses as binding. More recently, many reviews have extended the functional role of event-related gamma in the human brain (Başar, 2013; Başar et al., 2001; Başar-Eroglu et al., 1996; Herrmann et al., ,2004, 2010; Herrmann & Knight, 2001; Jensen et al., 2007; Singer, 1999; Tallon-Baudry & Bertrand, 1999). More specifically, gamma responses have been linked to episodic memory processes (Başar-Eroglu & Başar, 1991; Debener et al., 2003; Gruber et al., 2002; Herrmann et al., 2004; Kaiser et al., 2003; Karakaş et al., 2000; Miltner et al., 1999; Tallon-Baudry et al., 1998) and the elaboration of emotional valence of stimuli (Balconi & Lucchiari, 2008; Güntekin & Tülay, 2014; Keil et al., 1999, 2001, 2007; Luo et al., 2007, 2009; Martini et al., 2012; Müller et al., 1999; Sato et al., 2011). In addition, the causal role of brain systems generating gamma was highlighted in a recent review on the beneficial effects of interventions targeting gamma responses in patients with neuropsychiatric diseases (Struber and Herrmann, 2020).

Like other frequency bands, event-related gamma responses are affected by physiological aging (Arif et al., 2020; Barr et al., 2014; Böttger et al., 2002; Christov & Dushanova, 2016; Gaetz et al., 2012; Goossens et al., 2016; Herrmann & Demiralp, 2005; Hogan et al., 2011; Murty et al., 2020; Ross et al., 2010; Ross et al., 2020; Wiesmann and Wilson, 2019). For example, Böttger et al. (2002) showed lower phase-locked frontal gamma responses during a visual discrimination task in older CU participants.

Regional event-related gamma responses are also affected by pathological aging; however, findings vary according to the methodological approach used. On the one hand, Park et al. (2012) showed that mid-frontal gamma ERD during a spatial delayed match to sample task was lower in ADMCI compared to CU participants. Furthermore, Kurimoto et al. (2012) found that frontal and parietal gamma ERD during a modified Sternberg's task was lower in ADD relative to ADMCI patients. Another study by Fraga et al. (2018) showed that CU adults presented temporal and temporal-parietal gamma ERS during an N-back task, whereas ADMCI patients were characterized by temporal-parietal gamma ERD.

On the other hand, Osipova et al. (2006) showed that auditory 40 Hz steady state stimuli induced greater primary auditory cortex gamma power in ADD patients than CU participants. This effect was confirmed later in ADMCI patients (Van Deursen et al., 2011). Furthermore, Van Deursen et al. (2008) showed that gamma power during a checkerboard reversal task was greater in ADD than ADMCI patients and CU adults.

Başar, Emek-Savaş et al. (2016) showed that event-related posterior gamma responses during a visual oddball task were lower in ADD compared to CU participants in the early post-stimulus period (0–200 ms), with the opposite pattern observed later (400–600 ms). Furthermore, event-related gamma coherence during the same task was greater in ADD

TABLE 5 Event-related beta responses in ADMCI and ADD patients

	Participants	Task	Frequency beta	Results
Babiloni et al. (2000)	• 13 AD • 13 Older CU • 13 Young CU	Movement-related	Event-related (de) synchronization (ERD/ERS)	Greater Beta ERD in AD compared to CU during the movement Greater "post-movement" contralateral Beta ERS in CU compared to AD
Missonnier et al. (2007)	• 10 AD • 29 ADMCI • 13 Stable ADMCI (S-ADMCI) • 16 Progressive ADMCI (P-ADMCI) • 16 CU	n-back task	Event-related synchronization (ERS)	Lower ERS amplitude in P-ADMCI and AD compared to CU and S-ADMCI
Yener et al. (2009)	• 11 AD (unmedicated) • 11 AD (medicated) • 19 CU	Simple light task	Digital filtering (maximum peak-to-peak amplitude)	No difference
Başar et al. (2010)	• 19 Mild AD (unmedicated) • 19 Mild AD (medicated) • 19 CU	Visual oddball task Simple light task	Event-related coherence Sensory evoked coherence	No difference
Kurimoto et al. (2012)	• 13 AD • 13 ADMCI • 14 CU	Modified version of Sternberg's task	Event-related (de) synchronization (ERD/ERS)	Lower ERD response in AD patients compared to the CU in the right central area
Güntekin et al. (2013)	• 17 ADMCI • 17 CU	Visual oddball paradigm	EEG-evoked power, Inter-trial phase synchronization of beta responses Event-related beta responses	Evoked beta power: target and non-target difference diminished in ADMCI
Prieto del Val et al. (2015)	• 34 ADMCI • 16 ApoE ε4 carriers (ε4+) ADMCI • 18 ApoE ε4 noncarriers (ε4−) ADMCI • 26 CU	Associative memory The biographical matching task (congruent/incongruent famous faces and nonfamous faces) Conceptual priming task Visuospatial memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Cortical source imaging	Beta ERD: CU > ADMCI ε4+ ADMCI ε4−>ADMCI ε4+
Deiber et al. (2015)	• 45 ADMCI • 97 CU Upon 18-month neuropsychological follow-up: • 55 stable • (sCON) • 42 deteriorated (dCON)	Simple attentional task 2-back working memory task	ERD/ERS: event-related desynchronization/ synchronization, ITC: inter-trial coherence	Beta ITC: ADMCI < dCON, sCON Beta ITC: dCON < sCON Beta ERD: dCON > sCON

(Continues)

TABLE 5 (Continued)

	Participants	Task	Frequency beta	Results
del Val et al. (2016)	16 ADMCI-c: ADMCI individuals that, within a 2-year follow-up period, developed dementia • 18 ADMCI-s: Stable ADMCI • 26 CU	Famous or non-famous faces: • Encoding task • Conceptual priming task • Memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Volumetric measures were obtained for left and right sides of the hippocampus and amygdala	Beta ERD: CU>ADMCI both for the encoding (14–25 Hz; 0–1000 ms) and retrieval task (13.5–18 Hz; 700–1000 ms). During retrieval: ADMCI-s showed a greater correlation between beta ERD and associative memory in comparison with ADMCI-c
Fraga et al. (2017)	• 16 Mild AD • 21 ADMCI • 27 CU	n-back task	Event-related (de) synchronization (ERD/ERS)	Lower ERD response in AD and ADMCI compared to CU
Fraga et al. (2018)	• 15 Mild AD • 21 ADMCI • 27 CU	n-back task	Event-related (de) synchronization (ERD/ERS)	ADMCI were characterized by ERD while CU were characterized by ERS
del Val et al. (2018)	• 34 ADMCI • 16 ApoE ε4 carriers (ε4+) ADMCI • 18 ApoE ε4 noncarriers (ε4−) ADMCI • 26 CU	Associative memory The biographical matching task (congruent/incongruent famous faces and non-famous faces) Conceptual priming task Visuospatial memory task	Time-frequency: event-related desynchronization/event-related synchronization (ERD/ERS) Volumetric measures were obtained for left and right sides of the hippocampus and the intracranial volume	Beta ERD: CU > ADMCI ε4+
Koch et al. (2018)	14 Early AD	Transcranial magnetic stimulation (TMS)-evoked	Event-related spectral perturbation/Event-related power analysis Inter-trial coherence /Event-related phase locking analysis	Increased power and Increased ITC after rTMS condition
Mazaheri et al. (2018)	• 15 ADMCIconvertors group: Developed AD within 3-years • 10 ADMCI non-convertors group • 11 CU	Word comprehension task: Congruent or incongruent Category	Time-frequency representations (TFRs) of power Cross-frequency coupling between theta and alpha/beta	Beta suppression (15–20 Hz): ADMCI convertors>CU, ADMCI non-converters for semantic congruency. Increased late beta suppression associated with word congruency: ADMCI convertors>CU, ADMCI non-converters at the frontal area
Caravaglios et al. (2018)	• 15 ADMCI • 15 CU	Omitted tone task	Event-related spectral perturbation Inter-trial coherence	Beta power: CU > aADMCI Beta phase-locking: ADMCI > CU
Fodor et al. (2018)	• 17 ADMCI • 21 CU	Sternberg working memory task	Event-related spectral perturbation	Beta ERS: ADMCI< CU persons during retention

TABLE 5 (Continued)

	Participants	Task	Frequency beta	Results
Cespon et al. (2019)	• 14 AD • 12 CU	n-back task	Event-related power analysis	No significant difference
Serrano et al. (2020)	• 45 ADMCI • 49 SCD (Subjective cognitive decline) • 49 CU	Working memory task	Time-frequency analysis Event-Related Power	Beta power CU > ADMCI SCD > ADMCI
Tülay et al. (2020)	• 33 AD • 46 ADMCI • 48 CU	Visual oddball paradigm	Both evoked (phase-locked) and total (phase-locked + non-phase-locked) ERO powers	No statistical differences across the groups for beta responses

Abbreviations: ADMCI, Alzheimer's disease patients with mild cognitive impairment; ADD, Alzheimer's disease dementia; CU, cognitively unimpaired control; ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization.

(especially when patients had not undergone cholinergic therapy) compared to CU participants (Başar et al., 2017). Other studies found no differences in event-related gamma responses during cognitive tasks between ADD and CU controls (Koch et al., 2018; Tülay et al., 2020; Yener et al., 2009). Table 6 summarizes the results of event-related gamma responses in ADMCI and AD patients. The explored literature was insufficient for an evaluation of event-related gamma responses during cognitive tasks in patients with MCI and dementia not due to AD.

5 | DISCUSSION AND RECOMMENDATIONS

In this article, a multidisciplinary panel of experts reviewed the field literature and reached consensus about the event-related EEG oscillations during cognitive tasks more consistently found to be abnormal in ADMCI and ADD patients when compared to CU individuals and patients with MCI and dementia due to PD, LB, and VCI.

Previous EEG studies from independent research teams have consistently demonstrated *reduced event-related delta and theta power* in ADMCI and ADD patients during oddball tasks at the group level, relative to CU controls (Başar et al., 2010; Caravaglios et al., 2008, 2013; Cummins et al., 2008; Deiber et al., 2015; Güntekin et al., 2008, 2019; Karrasch et al., 2006; Michalopoulos et al., 2012; Tülay et al., 2020; Yener et al., 2008, 2012). Notably, these effects were not demonstrated at the individual level. Furthermore, they may be disease unspecific as similar abnormalities were observed in PDMCI (Güntekin et al., 2020; Yener et al., 2019), PDD (Güntekin et al., 2020), LBD (Rosenblum et al., 2020), and major VCI patients (Lou et al., 2011; Wang et al., 2016; Xu et al., 2011, 2015). Keeping the above data in mind, *the present Expert Panel recommends that event-related delta and theta power during oddball tasks may be used in future clinical trials carried out in ADMCI and ADD patients for analyses at the group level. Their use for diagnostic purposes is not recommended.*

Specifically, event-related delta and theta measures may be tested as prognostic biomarkers and endpoints of pharmacological and non-pharmacological interventions targeting the cognitive processes underpinning oddball paradigms, such as focused attention, decision making, and working memory (Donchin et al., 1973; O'connell et al., 2012; Polich & Kok, 1995). Indeed, considering the diagnosis of ADMCI and ADD based on clinical and standard diagnostic criteria for research (Jack et al., 2018), AD patients with the greatest alterations of event-related delta and theta power during oddball tasks may present the fastest clinical decline over time. Furthermore, AD patients with the smallest alterations in these EEG measures (i.e., the most preserved

TABLE 6 Event-related gamma responses in ADMCI and ADD Patients

	Participants	Task	Frequency gamma	Results
Osipova et al. (2006)	• 10 ADD • 12 CU	Auditory 40-Hz steady state	Event-related power	Greater 40 Hz power in ADD compared to CU
van Deursen et al. (2008)	• 15 AD (psychoactive drug naive) • 20 ADMCI (psychoactive drug naive) • 20 CU	Checkerboard reversal task	Event-related power	Greater Power in ADD compared to ADMCI and CU No difference between ADMCI and CU
Yener et al. (2009)	• 11 ADD (unmedicated) • 11 AD (medicated) • 19 CU	Simple Light task	Digital filtering (maximum peak-to-peak amplitude)	No difference
Missonnier et al. (2010)	• 29 ADMCI At 1-year follow-up; • 16 Progressive • ADMCI • -13 Stable ADMCI	*n*-back working memory task	Fractal analysis: fractal dimensions	Gamma fractal dimension during 2-back tasks: Stable ADMCI>Progressive ADMCI
van Deursen et al. (2011)	• 15 ADD (psychoactive drug naive) • 20 ADMCI (psychoactive drug naive) • 20 CU	Auditory 40-Hz steady state	event-related power	Greater 40 Hz power in ADD compared to ADMCI and CU
Park et al. (2012)	• 16 ADMCI • 19 CU	Spatial delayed match to sample (DMTS) task	ERSP (ERS/ERD)	Gamma event-related desynchronization: CU>ADMCI in the mid-frontal areas
Kurimoto et al. (2012)	• 13 ADD • 13 ADMCI • 14 CU	Modified version of Sternberg's task	Event-related (de) synchronization (ERD/ERS)	AD patients had lower ERD response compared to ADMCI in the left prefrontal and left medial parietal areas
Başar, Gölbaşı, et al. (2016)	• 15 ADD • 15 CU	Visual oddball task Simple light task	Digital filtering (maximum peak-to-peak amplitude)	Delayed event-related Gamma Response in ADD compared to CU Lower sensory-related early Gamma Amplitude over left hemisphere in ADD compared to CU
Başar et al. (2017)	• 21 Mild ADD (unmedicated) • 18 Mild ADD (medicated) • 21 CU	Visual oddball task Simple light task	Event-related coherence and Sensory-evoked coherence	Greater event-related and sensory-evoked Coherence in both ADD groups compared to CU in all sub-bands of gamma Greater event-related and sensory-evoked fronto-parietal gamma coherences in medicated ADD compared to unmedicated ADD Lower event-related occipito-parietal coherence in medicated ADD compared to unmedicated ADD
Fraga et al. (2018)	• 15 Mild ADD • 21 ADMCI • 27 CU	n-back task	Event-related (de) synchronization (ERD/ERS)	ADMCI were characterized by ERD while CU were characterized by ERS

(Continues)

TABLE 6 (Continued)

	Participants	Task	Frequency gamma	Results
Goodman et al. (2018)	• 33 ADD • 34 ADMCI • 31 CU	n-back task	Event-related theta-gamma coupling	Lowest theta-gamma coupling in AD (on 2-back task): AD < ADMCI < CU
Koch et al. (2018)	14 early ADD	Transcranial magnetic stimulation (TMS)-evoked	Event-related spectral perturbation /Event-related power analysis Inter-trial coherence /Event-related phase locking analysis	No difference
Jones et al. (2019)	3 CU	40 Hz light stimulus	Power spectral density	Increased 40-Hz gamma power after the 40 Hz-light stimulus
Zibrandtsen et al. (2020)	1,464 Patients	40 Hz intermittent photic stimulation (IPS)	Power spectrum analysis	Increased 40-Hz gamma power after the 40 Hz IPS at occipital area
Tülay et al. (2020)	• 33 ADD • 46 ADMCI • 48 CU	Visual oddball paradigm	Both evoked (phase-locked) and total (phase-locked +non-phase-locked) ERO powers	No statistical differences across the groups for gamma responses

Abbreviations: ADMCI, Alzheimer's disease patients with mild cognitive impairment; ADD, Alzheimer's disease dementia; CU, cognitively unimpaired control; ERO, event-related oscillation; ERS, event-related synchronization; ERD, event-related desynchronization.

neurophysiological cognitive systems) may yield the greatest benefit most from interventions targeting the neural underpinnings of focused attention, decision making, and working memory.

The above-mentioned EEG measures may also provide a functionally-specific complement to the measures derived from resting state condition. Notably, several commercial and open-access WEB-based EEG platforms (e.g., among others, see EEGlab at https://sccn.ucsd.edu/eeglab/index.php, LORETA at https://www.uzh.ch/keyinst/loreta.htmand, and Fieldtrip at https://www.fieldtriptoolbox.org/) are available for this purpose.

Figure 2 shows a schematic representation of the event related oscillatory abnormalities in ADMCI and ADD patients.

Previous EEG studies by independent research teams repeatedly showed that *non-phase locked alpha and beta ERD/ERS* in ADMCI and ADD patients were lower in magnitude than CU controls during cognitive tasks at the group level (Deiber et al., 2015; Fraga et al., 2017; Güntekin et al., 2019; Karrasch et al., 2006; Mazaheri et al., 2018; Michalopoulos et al., 2012; del Val et al., 2016). Similarly, some studies showed that ADMCI and ADD patients pointed to lower event-related beta power and phase-locking during cognitive tasks at the group level (Deiber et al., 2015; Güntekin et al., 2013; Missonnier et al., 2007). Finally, event-related gamma power and coherence during cognitive tasks were higher in ADD patients than CU controls at the group level, as a function of the post-stimulus period and frequencies considered (Başar, Emek-Savaş, et al., 2016; Başar et al., 2017; van Deursen et al., 2008, 2011). However, the EEG methodologies (i.e., alpha and beta ERD/ERS) and the cognitive tasks used (oddball, N-back, word recognition, etc.) were heterogeneous across the reviewed studies, which may limit the interpretation of findings. Furthermore, other studies showed contrasting evidence. Therefore, *the present Expert Panel recommends further clinical research before the use of event-related EEG oscillations at alpha, beta, and gamma frequency bands in clinical trials investigating ADD and ADMCI patients*. More research is also needed to systematically compare these measures across AD, PD, LBD, and VCI patient groups.

6 | LONGITUDINAL STUDIES USING EVENT-RELATED EEG RESPONSES FOR THE PREDICTION OF COGNITIVE DECLINE IN PEOPLE WITH AD AND PEOPLE WITH MCI OR OTHER DEMENTIA

Previous longitudinal studies have investigated event-related EEG responses in relation to cognitive decline in people with AD and people with MCI or dementia.

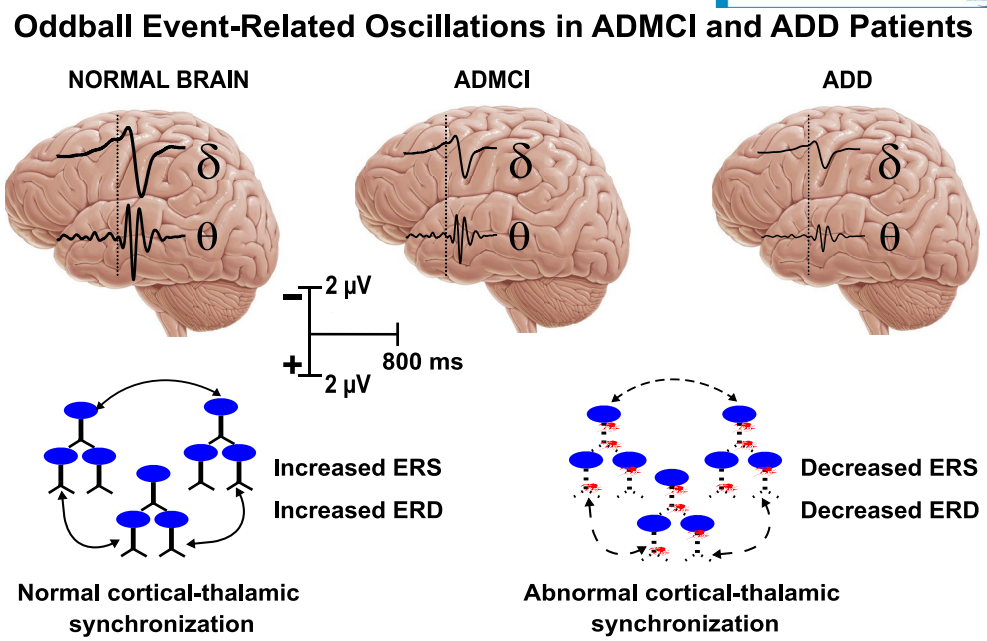

FIGURE 2 Schematic description of event-related alpha synchronization and desynchronization in cognitively unimpaired adults and ADD patients. In general, alpha ERS and ERD were both reduced in ADD patients

Concerning AD patients, Missonnier et al. (2006) showed reduced event-related theta power during an n-back working memory task in progressive ADMCI patients as compared to stable ADMCI patients and CU participants at one-year follow-up. Deiber et al. (2009) confirmed these results in a similar study investigating event-related EEG responses during an n-back task. They reported reduced frontal event-related theta power in progressive ADMCI patients as compared to stable ADMCI patients and CU participants. The same group (Deiber et al., 2015) carried out another study in which ADMCI patients and CU adults were clinically followed for 18 months. Based on clinical status at follow up, CU participants were divided into two groups: stable and deteriorated. At baseline, event-related theta responses during a 2-back working memory task were lower in the ADMCI patients than the stable CU group but there was no difference between the stable CU and deteriorated CU groups. In another study, Mazaheri et al. (2018) clinically followed ADMCI patients for three years. They reported that event-related theta power during a word comprehension task was lower in the progressive ADMCI patients (i.e., those who progressed to ADD), as compared to the stable ADMCI patients and the CU participants. Overall, the above findings confirm that reduced event-related theta responses during cognitive tasks not only reflect cognitive status in AD patients but they may also predict or monitor disease progression at the group level.

To our knowledge, only one study has investigated event-related EEG delta responses in ADMCI patients longitudinally. Emek-Savaş et al. (2016) showed that ADMCI patients who progressed to ADD after one year were characterized by poor event-related delta responses during a visual oddball task at the baseline recording session. Furthermore, as compared to CU participants and stable ADMCI patients, ADMCI patients progressing to ADD showed reduced event-related delta responses at 1-year follow-up. Though more research is needed in this area, current evidence suggests that event-related delta and theta responses may predict AD progression at the group level.

Longitudinal studies have also examined if alpha and beta event-related responses during cognitive tasks may predict or reflect AD progression. Prieto del Val et al. (2016) reported that ADMCI patients who progressed to ADD showed reduced alpha ERD during a memory encoding task as compared to CU participants and stable ADMCI patients. Mazaheri et al. (2018) tested ERD/ERS at various frequency bands during a verbal memory task in stable and progressive ADMCI patients (follow-up at three years). They showed that late alpha ERD diminished with repeated presentation of words in the CU group but not in stable and progressive ADMCI patients, thus indicating that such an EEG biomarker may reflect cognitive status but not AD progression.

In another longitudinal study, Missonnier et al. (2007) reported that baseline beta ERS recorded during an n-back task was lower in progressive (follow-up at one year) than stable ADMCI patients. Similarly, Prieto del Val et al. (2016) reported that progressive ADMCI patients (follow-up at two year) showed lower beta ERD during memory encoding at baseline as compared to stable ADMCI patients. In contrast, Mazaheri et al. (2018) found that beta ERD during a word comprehension task

at baseline was greater in progressive (follow-up at three year) than stable ADMCI patients. Finally, Deiber et al. (2015) showed that beta phase-locking during a 2-back working memory task at baseline was higher in the stable CU group compared to the deteriorated CU group (follow-up at 18 months).

The mixed results for alpha and beta frequencies may be due to a number of factors including the different EEG variables, time periods, and cognitive paradigms used. Overall, at baseline, beta ERS/ERD and phase-locking were generally lower in CU participants and AD patients who showed diminished cognitive status at follow-up (one year or later). Further longitudinal studies are needed, however, to reach conclusive recommendations about these frequencies.

Longitudinal studies examining event-related gamma responses in AD patients during cognitive tasks are also lacking. To our knowledge, there is only one study in the literature, conducted by Missonnier et al. (2010). The authors investigated gamma fractal dimensions of event-related EEG responses during a 2-back task; results showed that progressive ADMCI patients (follow-up at one year) were characterized by higher gamma fractal dimensions as compared to stable ADMCI patients, possibly reflecting reduced complexity of the EEG signal (Missonnier et al., 2010). Notably, mapping event-related gamma responses during cognitive tasks may help to inform potential treatments for AD patients based on neuromodulation of gamma, which is an emerging field. More specifically, both animal (Adaikkan et al., 2019; Iaccarino et al., 2016; Martorell et al., 2019) and human studies (Benussi et al., 2021; Ismail et al., 2018; Jones et al., 2019; Zibrandtsen et al., 2020) have shown potentially beneficial effects of electromagnetic or sensory stimulation at gamma frequencies in rodent models of AD and AD patients. Thus, event-related gamma responses during cognitive tasks may represent an informative intervention endpoint.

To our knowledge, there are no longitudinal studies investigating event-related delta, theta, alpha, beta, and gamma responses during cognitive tasks in non-AD older adults with MCI or dementia.

Considering the above review, *the present Expert Panel recommends that significant efforts be made to develop longitudinal studies investigating event-related EEG responses during cognitive tasks in older people with MCI and dementia due to Alzheimer's and related neurodegenerative disorders*. Such studies will dramatically improve our understanding of the extent to which EEG responses (including gamma) may provide heuristic measures of the natural deterioration of cognitive systems during disease progression, as well as sensitive biomarkers to demonstrate potential benefits of future smart drugs, cognitive training, and/or brain stimulation.

7 | MULTIMODAL STUDIES USING CSF, NEUROIMAGING, AND EVENT-RELATED EEG RESPONSES IN PEOPLE WITH AD AND PEOPLE WITH MCI OR OTHER DEMENTIA

Multimodal studies using CSF, neuroimaging, and event-related EEG responses during cognitive tasks are sparse in AD and non-AD patients with MCI or dementia. Results from existing studies are summarized in the following section.

In AD research, Prieto del Val et al. (2015) investigated event-related EEG responses during an episodic memory task in CU people and ADMCI patients (Prieto del Val et al., 2015). ADMCI patients with the most significant genetic risk factor of sporadic AD (i.e., ApoE ε4) showed reduced alpha ERD in temporal sources and less beta ERD in frontal sources, relative to CU people and ADMCI patients without ApoE ε4, thus suggesting reduced efficiency and capacity of memory-related information processing in the former group (Prieto del Val et al., 2015). In another study (del Val et al., 2018), the authors showed that in ADMCI patients with ApoE ε4, hippocampal damage affected episodic memory through temporal cortical thickness, event-related theta responses, and frontal alpha/beta ERD. In those ADMCI patients, the authors evaluated the predictive value of event-related EEG responses during an episodic memory task (del Val et al., 2016). As compared to CU and stable ADMCI groups, progressive ADMCI patients showed lower associative memory scores, larger atrophy of the medial temporal lobe, and lower capacity to recruit alpha oscillatory cortical networks (del Val et al., 2016). Interestingly, accuracy in predicting progression from MCI to dementia was higher using the encoding-induced abnormal alpha ERD in posterior cingulate sources at baseline compared to neuroimaging biomarkers of amygdala atrophy (del Val et al., 2016). When both neuroimaging and EEG biomarkers were used as an input, the best accuracy (about 80%) was reached (del Val et al., 2016). These findings extended previous magnetoencephalographic (MEG) evidence indicating that as compared to stable ADMCI patients, progressive ADMCI patients are characterized by lower episodic and semantic memory scores, larger atrophy of entorhinal cortex, and higher interdependence of source activity between anterior cingulate and temporo-occipital at alpha frequencies (López et al., 2014). Notably, this higher interdependence was associated with greater medial temporal atrophy and worse cognitive performance (López et al., 2014).

In another multimodal study, Fodor et al. (2018) investigated alpha-beta ERS/ERD during a Sternberg working memory task in ADMCI patients and CU participants. Structural MRIs were also carried out. Relative to the CU group, ADMCI patients showed reduced alpha and beta ERS

(Fodor et al., 2018). Furthermore, EEG source estimates showed that ADMCI patients were characterized by reduced beta ERS in inferior and middle temporal gyrus, fusiform gyrus, and cuneus. Furthermore, the correlation between EEG and structural MRI measures showed that beta ERS was correlated with the size of hippocampus, entorhinal cortex, and parahippocampal gyrus.

Serrano et al. (2020) investigated event-related theta, alpha, and beta (MEG) responses during a working memory task in ADMCI patients, those with subjective memory complaints, and CU participants. As compared to people with subjective memory complaints and those who were CU, ADMCI patients showed reduced theta, alpha, and beta power. Furthermore, ADMCI patients had lower hippocampal volume, with no differences between subjective memory complaints and CU groups. The authors also found significant positive correlations between theta-alpha power derived from EEG data and biomarkers of right precuneus and supramarginal gyrus as well as bilateral cingulate cortex, fusiform gyrus, and medial temporal lobe.

In a final study, Yener et al. (2016) investigated event-related EEG responses during an oddball task in CU and ADMCI groups. Structural MRIs were also carried out. Results showed that both event-related delta responses to the target stimuli and frontal volume were reduced in the ADMCI relative to the CU group. Additionally, the authors reported a linear reduction in frontal event-related delta responses and frontal lobe atrophy for CU and ADMCI participants as a whole group.

The results of this section support the idea that established multimodal fluid and neuroimaging biomarkers of AD are significantly associated with event-related EEG responses during attention and memory tasks. However, further cross-validation studies are needed to confirm the direct effects of AD-related amyloidosis, tauopathy, and neurodegeneration and their association with topography-specific event-related EEG responses. Confirming that association may lend further support to the use of EEG responses in the assessment of cognitive systems in AD patients.

Finally, *the present Expert Panel recommends the use of EEG source estimation techniques in the analysis of event-related delta and theta responses during oddball tasks in older people with MCI and dementia due to Alzheimer's and related neurodegenerative disorders*. Ideally, future EEG studies should use >48 scalp electrodes to mitigate spatial blurring of rsEEG source estimates (Babiloni, Barry, et al., 2020). In such studies, the exact location of electrode placement over the scalp can be digitized and integrated into realistic head models based on individual structural MRIs to enhance the spatial accuracy of rsEEG source estimates (Babiloni, Barry, et al., 2020). Estimated EEG source solutions may be especially suitable in multimodal studies in patients with MCI and dementia using neuroimaging techniques to map cerebrovascular lesions, core neuropathology, and neurodegeneration. Within a common brain space constructed by realistic MRI-based head models, abnormalities in EEG source solutions may be correlated with core neuropathology and neurodegeneration, as revealed by structural MRIs and PET or single-photon emission computerized tomography (SPECT), as well as clinical manifestations. Correlations between EEG biomarkers and specific features of Alzheimer's and related neurodegenerative disorders may elucidate the neurophysiological correlates of those disorders in the cognitively unimpaired brain.

8 | INTERNATIONAL INITIATIVES FOR RESEARCH ON RSEEG MEASURES IN AD

In general, the findings reviewed in the present article raise the need for international consensus initiatives to develop or refine a multicenter standardization of instructions to patients, EEG recordings during oddball tasks, and selection of artifact-free rsEEG periods in line with the standards of clinical trials in AD. First attempts can be found in initiatives of the International Federation of Clinical Neurophysiology (Babiloni, Barry, et al., 2020; Rossini et al., 2020) as well those of the Electrophysiology Professional Interest Area of ISTAART.

The present Expert Panel recommends the development of comprehensive EEG experiments comparing event-related delta and theta responses during oddball tasks among groups of patients MCI and dementia due to AD, PD, LB, and VCI. A key feature of those future studies may be the longitudinal multicenter enrollment of patients and use of standard methods for the computation of phase-locked EROs at delta and theta bands. Two interesting examples are shown in Colclough et al. (2016) and Mahjoory et al. (2017).

Despite several evidence-based reviews (Lejko et al., 2020; Yener & Başar, 2010, 2013), no substantial study has been reported testing the discriminative power of event-related EEG oscillatory responses during cognitive tasks at the individual level in AD, PD, LBD, and VCI patients. Therefore, while these measures are not yet suitably validated for diagnostic, screening and progression tracking use-cases, we recommend machine learning and other discriminative analyses be applied both to future studies, and retrospectively to some of the high-quality data sets already collected. When performing these analyses, we also recommend that hypothesis driven approaches to data characterization (e.g., functional connectivity and other graph-related measures) be applied, alongside deep learning and other feature discovery approaches.

9 | CONCLUSIONS

How should we frame event-related EEG oscillations in the theory of AD biomarkers? It is well know that the Working Group of the National Institute of Aging and Alzheimer's Association (NIA-AA) Research Framework (Jack et al., 2018) proposed two classes of biomarkers for AD research: (i) *diagnostic Alzheimer's disease* biomarkers, measuring cerebral amyloidosis (i.e., "A" biomarkers) and phospho-tau (i.e., "T" biomarkers) by CSF or PET techniques and (ii) *neurodegenerative/progression* biomarkers (i.e., "N" biomarkers), measuring total tau by CSF sampling, FDG-PET hypometabolism, and structural MRI markers of brain atrophy. Keeping in mind the above theoretical qualification of AD biomarkers, the present Expert Panel posits the introduction of another class of biomarkers in the instrumental assessment of AD patients. These biomarkers may probe the vulnerability or resilience of *subcortical and thalamocortical neural (de)synchronization mechanisms* in relation to AD processes. For the purposes of the present study, the biomarkers of event-related EEG oscillations may be represented by the mentioned *event-related delta and theta power during oddball tasks*. Keeping in mind the *neurophysiological* meaning of these EEG biomarkers, the term *neural synchronization or physiological biomarker* (i.e., "P" biomarker) may be introduced in the above A-T-N Research Framework (Jack et al., 2018).

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CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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