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A Systematic Review of Cognitive Event-Related Potentials
in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

This systematic review examined whether event-related potentials (ERPs) during higher cognitive processing can detect subtle, early signs of neurodegenerative disease. Original, empirical studies retrieved from PsycINFO and PubMed were reviewed if they analyzed patterns in cognitive ERPs (≥ 150 ms post-stimulus) differentiating mild cognitive impairment (MCI), Alzheimer's disease (AD), or cognitively intact elders who carry AD risk through the Apolipoprotein-E $\epsilon 4$ allele ($\epsilon 4+$) from healthy older adult controls (HC). The 100 studies meeting inclusion criteria (MCI=47; AD=47; $\epsilon 4+=6$) analyzed N200, P300, N400, and occasionally, later components. While there was variability across studies, patterns of reduced amplitude and delayed latency were apparent in pathological aging, consistent with AD-related brain atrophy and cognitive impairment. These effects were particularly evident in advanced disease progression (i.e., AD > MCI) and in later ERP components measured during complex tasks. Although ERP studies in intact $\epsilon 4+$ elders are thus far scarce, a similar pattern of delayed latency was notable, along with a contrasting pattern of increased amplitude, consistent with compensatory neural activation. This limited work suggests ERPs might be able to index early neural changes indicative of future cognitive decline in otherwise healthy elders. As ERPs are also accessible and affordable relative to other neuroimaging methods, their addition to cognitive assessment might substantively enhance early identification and characterization of neural dysfunction, allowing opportunity for earlier differential diagnosis and targeting of intervention. To evaluate this possibility there is urgent need for well-powered studies assessing late cognitive ERPs during complex tasks, particularly in healthy elders at risk for cognitive decline.

Keywords: Event-related potentials, Alzheimer's disease, mild cognitive impairment, Apolipoprotein-E ϵ 4, biomarkers, electroencephalography

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that is closely associated with an accumulation of beta-amyloid plaques, neurofibrillary tangles, and brain atrophy [113]. Symptoms of the disease include marked cognitive decline from baseline functioning in areas such as planning, problem solving, memory, language, and orientation, as well as impairment in completing instrumental activities of daily living [2]. Mild cognitive impairment (MCI) is considered a prodromal form of AD due to the comparable though less severe neuropathology and cognitive decline; approximately 10% of those with MCI convert to AD each year [17]. Early detection is especially important in AD as its neuropathological hallmarks may be present decades before onset of symptoms [2,9]. One primary factor associated with risk for AD is carrying the Apolipoprotein-E (APOE) $\epsilon 4$ allele. Those who carry one of two copies of the $\epsilon 4$ allele have a 3-4x greater than average risk of AD, while those who carry both $\epsilon 4$ alleles have 10x greater risk [141].

The investigation of neural biomarkers, such as those using neuroimaging measures for AD is an important and burgeoning field. A biomarker is a measure that offers an objective index of structural or functional differences that can be used to predict or track a disease [134]. Although methods such as functional magnetic resonance imaging (fMRI) dominate the literature, electroencephalography (EEG) and event-related potentials (ERPs) hold particular promise due to their accessibility, affordability, and superior temporal specificity compared with other neuroimaging modalities. Thus, ERPs could be a valuable addition to cognitive assessment in identifying and tracking disease onset and progression.

EEG is a neurophysiological methodology in which electrical activity of the brain (i.e., summed postsynaptic potentials) is recorded via electrodes placed on the scalp. ERPs are an application of EEG that specifically time-lock such electrophysiological activity to a stimulus or a behavioral response. The amplitude and latency of changes in voltage provide insight into the magnitude and timing of information processing in the brain [87,136]. The present systematic review focuses on 'cognitive' ERPs occurring at least 150ms post-stimulus, reflecting higher order cognitive processes such as executive functioning, memory encoding and retrieval, and semantic processing [102]. Previous research on earlier sensory components has relatively consistently revealed intact early components in groups with AD compared to healthy older adult groups, suggesting that more automatic perception of stimuli may remain intact, while more complex cognitive processing of such stimuli declines, at least in mild to moderate AD [51,78,102]. Considering ERPs as biomarkers of AD-related neuropathology could expand upon the spatial knowledge provided by structural and functional MRI studies and enhance understanding of the temporal nature of communication and connectivity of neural networks associated with AD.

Most recent neuroimaging studies have used MRI, fMRI, and positron emission tomography (PET) to examine MCI and AD. Overall, AD studies demonstrate reduced regional brain volume and cortical thickness, and decreased activation in the amygdala, hippocampus, inferior and medial temporal lobes, anterior cingulate cortex, and regions of the prefrontal cortex (e.g., orbitofrontal) and parietal lobes [79,98,119] relative to typical aging. Additionally, while typical aging may be accompanied by a widespread decline in functional connectivity, exaggerated decline is observed in those with AD, especially in regions associated with the

default mode network, such as posterior cingulate cortex, medial prefrontal cortex, inferior parietal lobules, lateral temporal cortices, and the hippocampi [37]. Findings in MCI are more varied, sometimes indicating increased activation and other times indicating decreased activation in AD-relevant regions, such as the medial temporal lobe and the default mode network. This variability is largely attributed to task differences (e.g., cognitive demand) and variation in MCI and AD severity across studies [33,153].

Studies of early indicators of neural decline in healthy, cognitively intact APOE $\epsilon 4$ carriers compared to non-carriers are scarce. The available research with fMRI suggests that cognitively intact $\epsilon 4$ carriers exhibit a period of increased, compensatory activation relative to their lower risk counterparts [14,121,130]. Yet, over time, activation in $\epsilon 4$ - steadily increases while in $\epsilon 4+$ it decreases, becoming more comparable with what is seen with MCI and AD, indicative of advancing neuropathology [121].

Whereas fMRI has exceptional spatial localization, ERPs compliment and expand upon this research by providing a more direct and temporally precise understanding of neural processes. While fMRI signals are a proxy for neural activity, generated seconds afterward by capillary-level blood oxygenation, ERPs directly capture neuronal activity with millisecond-level precision [85,87]. Furthermore, individuals that are unable or unwilling to undergo MRI scans can still participate in EEG sessions. This non-invasive and relatively low-cost option is viable for individuals with medical devices such as pacemakers, joint replacements and other implants, high body mass index, tattoos, extensive dental work, and anxiety about confined spaces. These advantages make EEG and ERPs particularly appealing as a form of early detection of AD risk.

This present study is a systematic review of MCI, AD, and intact APOE ϵ 4-carrier groups relative to healthy controls with ERPs reflecting higher cognitive functions (defined herein as >150 ms post-stimulus onset). While reviews of ERPs in AD have been conducted [65,102], none to date have been systematic reviews. Although a 2017 paper examined ERPs associated with MCI [58], the present review adds studies published since that paper; assesses AD and APOE studies in comparison with MCI; and focuses and expands evaluation of later, cognitive ERP components. The present review therefore systematically highlights specific patterns in the literature relative to each individual component examined, investigates variability and contradictory results; evaluates demographic and task-related variables that may account for variable findings; and discusses pattern similarities and differences across components that can help direct future research attempting to distinguish these groups.

2. Methods

2.1 Search strategies

Database searches were conducted in PsycINFO and PubMed for peer-reviewed articles in the English language. MCI searches using the keywords ["ERP" OR "event-related potential"] combined with ["MCI" OR "mild cognitive impairment"] returned a combined 169 results (69 PsycINFO; 100 PubMed). To assure comprehensive coverage, all 42 studies from Gu and Zhang's review [58] were added to the initial return list, resulting in a complete initial list of 211 studies. Alzheimer's disease and APOE searches were conducted using the keywords ["ERP" OR "event-related potential"] combined with ["Alzheimer's" OR "APOE" OR "Apolipoprotein E"]. These search terms turned out a combined 379 initial articles (153 PsycINFO; 226 PubMed). Notably,

there were far fewer initial returns for APOE/Apolipoprotein-E searches (20) compared to Alzheimer's or MCI (359 and 211, respectively).

2.2 Article Selection

Figure 1 displays the overall process for study exclusion. As the first step of article evaluation, duplicate articles were deleted. The remaining returns were then evaluated based on title and abstract, and were only included in the next step if they: 1) were original, empirical studies, 2) analyzed cognitive event-related potentials (i.e., 150ms post-stimulus or later), 3) employed a sample of participants with MCI, AD, or intact participants deemed at risk for AD as carriers of the APOE ϵ 4 allele, and 4) compared an MCI/AD/APOE ϵ 4 group with a healthy older adult control group. Studies that survived this title and abstract review were subjected to full article evaluation. Studies excluded at this phase failed criteria for the following reasons: non-empirical study (n=16), no between-group comparison of cognitive ERPs (n=20), no AD/MCI group (n=12), no healthy older adult control group (n=12), a sample size < five participants per group (n=1), use of non-traditional MCI subjects (e.g., MCI in stroke patients; n=3), and single trial methodology not comparable with other studies (n=1). Note that some excluded papers failed multiple inclusion criteria, but each was recorded under one category for simplicity. The final samples included in the review were 47 MCI, 47 AD, and 6 APOE ϵ 4 studies.

Figure 1. Article selection process for a. MCI studies, and b. AD and APOE $\epsilon 4$ studies.

3. Results

The 47 MCI, 47 AD, and six APOE studies reviewed herein are described in Table 1 (MCI) and Table 2 (AD, APOE). These studies overall identified several cognitive ERP components that may be altered in the progression of AD-related neuropathology. The most frequently investigated components were N200 (21 MCI, 13 AD, 4 APOE), P300 (30 MCI, 33 AD, 5 APOE), and N400 (6 MCI, 16 AD, 1 APOE). Although rarely investigated, some studies examined the late positive component (LPC, aka P600), the parietal old/new effect, late slow waves, the late positive potential (LPP), and some other uncommon components (e.g., N250r, C250, contingent negative variation (CNV)). Study of components with less than three supporting articles are not comprehensively discussed [e.g., 21,24,27,44], but are included in Tables 1 and 2.

[Table 1]

[Table 2]

3.1 Study Characteristics

3.1.1 Sample Size

Study demographics and other characteristics are shown in Table 3 (MCI) and Table 4 (AD, APOE). This review covers a total of 3,922 participants (2,359 MCI v. HC; 1,445 AD v. HC; 118 APOE $\epsilon 4+/-$). Within each study type (MCI, AD, or $\epsilon 4$), sample size was not significantly different between the comparison groups (MCI v. HC: $t(47) = 1.5, p=.15$; AD v. HC: $t(44) = -0.7, p=.52$; $\epsilon 4+ v. \epsilon 4-: t(4) = 1.0, p=.37$). However, across study type, sample size was significantly different ($F(2,95) = 15.4, p<.001, \eta_p^2 = .25$). MCI studies had significantly larger samples ($ps <.001$; $M_{MCI} = 25.9, SD = 14.5, MED = 22.5, range = 5-91$; $M_{HC} = 23.2, SD = 11.0, MED = 20, range = 6-63$) than AD studies ($M_{AD} = 15.2, SD = 7.1, MED = 14, range = 6-36$; $M_{HC} = 15.6, SD = 6.7, MED = 15, range = 8-39$) and $\epsilon 4$ studies ($M_{\epsilon 4+} = 12, SD = 5.1, MED = 10, range = 9-21$; $M_{\epsilon 4-} = 11.6, SD = 4.8, MED = 10, range 8-20$), which did not significantly differ. Some MCI studies subdivided their samples by MCI type, resulting in group sizes generally more comparable to those in AD studies.

[Table 3]

[Table 4]

3.1.2 Group Ages

Most but not all studies reported group age statistics. Between study type (MCI, AD, or $\epsilon 4$), average age did not significantly differ ($F(2,71) = 1.2, p>.10, \eta_p^2 = .03$). However, the average age of the comparison groups was significantly different across investigations ($F(1,71) =$

9.5, $p < .003$, $\eta_p^2 = .12$). Specifically, healthy controls tended to be younger than the diagnostic group in both studies of MCI ($t(32) = 5.4$, $p < .001$; $M_{\text{MCI}} = 71.3$, $SD = 3.8$, range = 64.4-79.9; $M_{\text{HC}} = 69.5$, $SD = 4.1$ range = 61.6-77.6) and studies of AD ($t(36) = 3.3$, $p < .002$; $M_{\text{AD}} = 72.9$, $SD = 4.5$, range = 65.2-82.4; $M_{\text{HC}} = 71.0$, $SD = 2.1$, range = 64.4-77.5). In the small number of $\epsilon 4$ studies, age was similar across comparison groups ($t(3) = 0.95$, $p = .42$; $M_{\epsilon 4+} = 72.7$, $SD = 3.2$; range = 69.6-75.7; $M_{\epsilon 4-} = 71.6$, $SD = 2.6$; range = 69.0-75.3). The actual differences between comparison groups may even be greater than we report, since some studies could not be tabulated due to only reporting age ranges; in some cases there were greater extremes than we report (e.g., MCI studies youngest reported age was 40 years).

3.1.3 MMSE Scores

The Mini-Mental State Examination (MMSE) was used in most studies to assess general cognitive functioning [41], although group scores were reported in only 38/47 (i.e., 81%) MCI studies, 28/47 (60%) AD studies, and 2/6 (33%) APOE studies. The two APOE studies that reported MMSE scores had an average score of 27.6 ($SD = 0.85$) in $\epsilon 4+$ groups and 27.32 ($SD = 1.68$) in $\epsilon 4-$, consistent with intact performance. As would be expected, average MMSE score was lower in diagnostic groups than in controls ($F(1,51) = 57.5$, $p < .001$, $\eta_p^2 = .53$), with MCI lower than within-study controls ($M_{\text{MCI}} = 26.7$, $SD = 1.4$, range = 23.1-28.4; $M_{\text{HC}} = 28.9$, $SD = 0.5$; range = 28.0-29.7; $t(24) = -8.6$, $p < .001$) and AD lower than within-study controls ($M_{\text{AD}} = 21.6$, $SD = 2.7$, range = 16.5-27.0; $M_{\text{HC}} = 28.7$, $SD = 1.0$; range = 24.6-29.8; $t(27) = -15.3$, $p < .001$). Furthermore, the severity difference between AD studies and MCI studies for the diagnostic groups ($p < .001$) but not control groups ($p = .50$) was verified by a significant interaction ($F(1,51) = 83.3$, $p < .001$, $\eta_p^2 = .62$). Yet, we note overlap of MCI, AD, and HC ranges of MMSE scores that

may have contributed to differences in study outcomes (see Tables 3 and 4). For example, Pedroso et al.'s [111] HC group had a mean MMSE score of 24.60 ($SD = 4.0$), which was comparable with many of the AD groups in other studies, while Jacob and Duffy's [69] AD group had an average score of 27 ($SD = 0.7$), exceeding the mean of many HC groups in other studies.

3.1.4 Task Paradigms

Oddball paradigms were the most frequently used task across all groups, accounting for 41% of MCI (16/47), 49% of AD (23/47), and 33% of APOE (2/6) studies; most of these were auditory oddball tasks (75% of MCI, 96% of AD, 100% of APOE). Oddball tasks are characterized by frequently presenting a standard stimulus (e.g., 500Hz tone), and occasionally presenting a novel stimulus (e.g., 1,000Hz tone). Most of the oddball paradigms reviewed here required a response to novel stimuli (e.g., button press), although some were passive tasks with no response. In both cases, oddball paradigms have low cognitive demand, assessing attention and novelty detection [35]. Novel stimulus presentation is commonly associated with N200 and P300 peaks. Indeed, 61% of the studies analyzing N200 (i.e., MCI: 9/19, AD: 11/13, APOE: 2/4) and 57% of those analyzing P300 (i.e., MCI: 15/30, AD: 22/33, APOE: 2/5) used oddball tasks. Other low-demand tasks employed in the studies of this review included single-stimulus identification tasks in auditory, visual, and olfactory modalities (one AD study, 3 of 6 APOE studies), which also analyzed N200 and/or P300 components, and one MCI study that used a visual tool-using gesture task and focused on the P300 component.

Working memory tasks were used in 12% of the studies reviewed, most of them in MCI studies (i.e., MCI: 10/47, AD: 2/47, APOE: 0/6). Working memory includes storing, manipulating, and updating information in the short-term memory store; this is also one of the facets of

executive functioning [6]. Studies reviewed here used tasks such as n-back, delayed match-to-sample (DMS), and Sternberg paradigms. These working memory tasks highlight the relevance of N200 and P300 beyond simpler oddball paradigms, with 7/12 working memory studies analyzing N200 and/or P300. The remaining components examined relative to working memory included less frequently studied ERPs such as C250, N250r, P450, the late positive component (LPC), and the late positive potential (LPP).

Executive functions are a collection of higher-order cognitive processes responsible for organizing and adapting goal-oriented behavior, including processes such as inhibitory control, task-switching, and updating of working memory [91]. Only 15% of the 100 studies reviewed examined these tasks. Twelve MCI studies used them (i.e., 26%, 12/47), including go/no-go, Stroop, flanker, and task-switching paradigms. As with oddball and working memory-specific studies, these studies primarily analyzed N200 and P300 components. Some included less frequently studied N200 subcomponents such as N2pc and N2cc, and two studies also analyzed later slow wave potentials. Notably, almost all of these studies were done in MCI; only three AD studies (6%; selective attention and flanker tasks), and no APOE studies, used executive functioning tasks.

Semantic processing involves encoding, storage, and retrieval of meaning associated with concepts and categories, and episodic memory examines delayed retention and retrieval of recently learned memory sets [140]. These higher-order tasks have seen less frequent ERP study than simpler tasks; overall, 28% of the studies reviewed included them. A much smaller proportion of MCI studies (i.e., 4/47; 9%) used semantic tasks, compared with AD studies (i.e., 17/47; 37%). Most of these (88%) examined the N400 component, which is associated with

language, semantic processing, and recognition memory [77]. Some of the studies also included LPC, N300, and P300 components. Only one of the six healthy APOE group studies (17%) also used a semantic task, examining N400. This was the most complex of the tasks, and the latest ERP component employed with these healthy subjects. Finally, six studies examined episodic memory (MCI: 4/47, AD: 2/47), primarily focusing on N400, and other late components (e.g., LPP, late frontal effect (LFE), parietal effect (PE)).

3.1.5 Electrode Sites

The vast majority of studies, particularly those analyzing N200 and P300 components, analyzed only midline electrodes (N200: 80% of studies providing electrode information, MCI: 15/18, AD: 9/13, and APOE: 4/4; P300: 77%; MCI: 21/29, AD: 25/32, and APOE: 5/5). Lateral sites, however, may be uniquely sensitive to age- and AD pathology-related neural changes [18,108,122]. Indeed, one study with healthy APOE groups [74] found compensatory activation only in the right, non-task dominant hemisphere in APOE ϵ 4 carriers. Lateral electrodes may also best detect group differences for particularly lateralized tasks, since midline electrodes might underestimate or exclude lateral activity, depending on source distance from midline. For example, in a tool-using gesture paradigm [23], AD differed from HC on P300 amplitude at six lateral electrodes (i.e., F3, F4, C3, P3, T5, T6), but only one midline electrode (i.e., Pz).

Overall, group differences were generally found at sites consistent with typical component maxima, where reported. For example, with N200, including both fronto-central and parietal electrodes, revealed differences between MCI and HC groups; these reflect different underlying processes in N200 and may be differentially impacted by pathological aging processes [40,128]. P300 differences were primarily found at parietal sites (the usual maxima)

and sometimes at centro-parietal sites. Yet, adding frontal electrodes was revealing in the studies that did so, in part due to capture of anterior age-related shifts [34]. Specifically, frontal electrodes frequently added group discrimination for N200, P300, N400, and LPC components, in addition to findings at component-specific maxima sites. This was particularly notable for N400, despite its typically centro-parietal maxima. Similar frontal shift-related effects were apparent in some P300 studies, but P300a and P300b were rarely distinguished, which would be important in order to draw meaningful conclusions. Notably, few AD studies reported the loci of group differences. Finally, some studies combined electrodes (i.e., ROI approach), but the number of electrodes combined was much larger for late than for early components. Specifically, N200 and P300 ROIs typically included 3 to 4 electrodes (group averages = 3.0 to 4.1). In contrast, ROIs for N400 and LPC included 2 to 7 times more electrodes (N400 group average ranged from 11 to 32; LPC group average ranged from 13.2 to 14), making the source of these ROIs much less specific.

3.2 Event-Related Potential Results

An overview of the general pattern of findings for all ERP components investigated by at least three studies in this review are summarized in Table 5. The most common trends within each component are summarized by diagnostic group to highlight patterns both within and across groups. Toward capturing non-majority patterns that may impact future research, trends evident in the remainder of the studies are also summarized within each ERP component and diagnostic group.

[Table 5]

3.2.1 N200

The N200 component is a negative-going wave that typically peaks within 100-300ms post-stimulus and can be broken down into two subcomponents: N200a (i.e., the mismatch negativity; MMN) and N200b. N200a is thought to reflect automated sensory processing, specifically in response to novel stimuli [109]. N200b tends to index conscious and intentional attention to stimuli, especially those that deviate from the expected stimulus (e.g., oddball paradigms) [109]. Within inhibitory control paradigms, N200b also reflects alerting to the need to activate inhibition preceding motor inhibition [56,66]. While many studies investigating the N200 component did not separate N200a and N200b, those that specifically isolated N200a (i.e., mismatch negativity) were excluded from the present review due to the earlier, more automatic and sensory nature of this component [109,115]. Comprehensive reviews of the N200a subcomponent with age and AD have already been reported [25,112]. A few studies assessed specific subcomponents of the N200 ERP including N2pc, N2cc, and N250r [20-22,26,36]. Given the limited research with these ERPs they are not discussed in the review; see Tables 1 and 2 for individual study details in MCI and AD, respectively.

3.2.1.1 MCI Amplitude. Eighteen studies assessed N200 amplitude in MCI compared to healthy controls, of which 12 reported no significant group differences [i.e., 67%; 11,22,28,51,53,78,81,83,86,94,120,142]. Of those that detected significant group differences (i.e., 6/20 total studies), the majority reported smaller N200 amplitudes in MCI compared to HC [i.e., 67% significant studies; 22% total studies; 12,29,30,145]. One further reported that N200 amplitudes were smallest in progressive MCI compared to non-progressive MCI and healthy controls [12]. These studies primarily used more complex tasks than the traditional oddball

paradigm, including Go/No-Go and Flanker tasks (i.e., 3/4; 75%). Of the 12 studies that did not detect group differences, 50% used simple visual or auditory oddball paradigms, suggesting that differences in N200 amplitudes may not be sufficiently evident using simple oddball paradigms. The remaining two studies, both from the same laboratory, in fact reported *larger* N200 amplitudes in the MCI group [i.e., 11%; 106,107]. One of these studies used particularly uneven sample sizes, with 91 MCI participants and 30 HC [106]. Notably, these MCI participants were at the young end of the range for these studies and at the high end for MMSE. This may reflect early compensatory activation that precedes decline [108,122].

3.2.1.2 AD Amplitude. Eleven studies analyzed N200 amplitude differences between AD and HC, nine of which reported no significant between-group differences [i.e., 82%; 31,60,63,69,73,92,110,118,142]. All but one of these studies employed auditory oddball tasks. In contrast, the two studies that reported significant differences both used more complex executive function tasks; both demonstrated smaller N200 amplitudes in AD compared to HC groups [i.e., 18%; 84,145]. Specifically, Wang et al. [145] used the Erickson Flanker Task and Lockwood et al. [84] used an attentionally cued orientation discrimination task. Both of these tasks tap inhibitory control and attention in a visual modality, thereby differing in both modality and stimulus complexity from an auditory oddball paradigm.

3.2.1.3 Cognitively Intact APOE ϵ 4 Carriers Amplitude. Four of the six APOE studies investigated N200 amplitude; all four reported no significant differences between ϵ 4 carriers and non-carriers [39,54,93,147]. Yet, all studies used simple auditory oddball or odor identification tasks, which as noted even with MCI and AD where cognitive symptoms are present, may not be ideal for detecting AD-related differences in N200 amplitude. Furthermore,

most of these studies had small samples (e.g., nine per cell), indicating low power in detecting subtle group differences in intact groups.

3.2.1.4 MCI Latency. Ten of the 19 MCI studies assessing N200 latency reported no significant between-group differences [i.e., 53%; 28,29,51,78,81,83,86,106,120,142]. Of those that did detect significant differences, all nine reported prolonged latencies in MCI compared to healthy control groups [i.e., 47%; 11,12,22,30,53,90,94,107,145]. Missonier and colleagues further specified that N200 latencies were prolonged in progressive MCI compared to both non-progressive MCI and healthy controls [90]. Several of the studies that reported non-significant results might have lacked sensitivity due to uneven sample sizes and/or differences in average age between groups.

3.2.1.5 AD Latency. Of the twelve studies that investigated N200 latency in AD, six reported prolonged N200 latencies in the AD group (i.e., 50%; five statistically significant, [i.e., 42%; 92,96,110,118,135], one trending [i.e., 8%; 145]). Five studies found no significant between-group differences [i.e., 42%; 31,60,69,84,150], though they had small samples, high AD MMSE scores (i.e., low impairment), and/or differences in age between groups. Hirata and colleagues [63], in contrast to all other studies, reported significantly *shorter* latencies in AD participants.

3.2.1.6 Cognitively Intact APOE ϵ 4 Carriers Latency. Four APOE studies examined group differences in N200 latency. Three reported significantly prolonged N200 latency in ϵ 4 carriers relative to non-carriers, including delayed N200 latencies in ϵ 4+ compared to ϵ 4- within a sample with a positive family history of AD [54]. Two studies showed delayed N200 latencies in ϵ 4+ groups with olfactory identification tasks, but not during visual or auditory oddball

paradigms. The remaining study demonstrated prolonged latency in $\epsilon 4/\epsilon 4$ (i.e., homozygotes; very high risk) compared to $\epsilon 4/\epsilon 3$ (i.e., heterozygotes; high risk). Yet, $\epsilon 4$ homozygotes only differed from low risk $\epsilon 3/\epsilon 3$ (i.e., $\epsilon 4$ -) participants at a trend level [39]. The samples in all these studies were quite small, precluding strong conclusions.

3.2.2 P300

The P300 component is a positive-going wave that peaks between 250-700ms post-stimulus. As with the N200 component, P300 is divided into P300a and P300b subcomponents. P300a generally occurs within 250-280ms, tends to have a fronto-central maxima, and is associated with novel stimulus detection (i.e., infrequent perceptual stimuli in oddball paradigms), which may be modulated by attentional demand [117]. P300b tends to peak around 250-500+ms with a parietal maxima, and is associated with aspects of executive functioning, such as updating of working memory, subsequent memory storage, inhibitory control, and selective attentional processes [4,109,117]. P300 has been the frequent target of ERP studies, including in the limited literature on MCI and AD. The majority of the studies assessing the P300 component in this review did not specify P300a vs. P300b. Thus, results and interpretation could not be divided by subcomponent.

3.2.2.1 MCI Amplitude. Sixteen of the 29 total studies assessing P300 amplitude in MCI reported no significant difference between groups [i.e., 55%; 11,22,28-30,46,51,78,94,105-107,114,133,139,142]. Of the remaining 13 studies that reported group differences (i.e., 45%), 11 reported smaller P300 amplitudes in MCI compared to HC groups [i.e., 85% of significant studies; 38% of total studies; 12,23,53,57,59,81,83,86,138,145,148], including one that specified smaller amplitudes in progressive MCI compared to both non-progressive MCI and healthy controls [12]. Of the studies that detected group differences, 73% used more complex

executive functioning tasks (e.g., N-back, Go/No-go). In contrast, 72% of the studies that reported no group differences used oddball tasks, and two of the studies that did report differences using oddball paradigms had particularly large sample sizes [12,83]. The remaining two studies demonstrated larger P300 amplitudes in the MCI group [i.e., 7%; 82,120], but both studies were unique in that they compared P300 condition/stimulus difference waves instead of un-subtracted waveforms. These two studies specifically highlight abnormally enhanced P300 amplitudes to less relevant stimuli (e.g., non-match vs. match) in MCI, in contrast to HC who appropriately devoted more resources to processing novel and relevant stimuli [82,120]. These two studies were therefore consistent with the other studies reporting MCI differences. Thus, at least when more complex tasks were employed with reasonable statistical power, P300 amplitude discriminated between groups, reflecting underlying neural deficits in MCI.

3.2.2.2 AD Amplitude. The majority of the 25 studies that analyzed P300 amplitude reported smaller amplitude in AD compared to HC groups [i.e., 60%; 3,4,13,42-43,60,63,71,84,89,114,118,142,145,152], including one reporting a trend that did not reach statistical significance [42]. The remaining ten studies reported no significant difference between groups [i.e., 40%; 31,47,69,72-73,92,105,110,126,139]. These latter AD studies were notable for small sample sizes (e.g., eight per cell), age differences between groups, high AD group MMSE scores (e.g., 27/30), and/or simple tasks (i.e., 67% oddball paradigms), which may have limited power to detect group differences.

3.2.2.3 Cognitively Intact APOE ϵ 4 Carriers Amplitude. Four studies assessed APOE group differences in P300 amplitude; none detected significant group differences. It was, however, difficult to draw conclusions from these studies. Beyond their small number, the use

of small samples and simple tasks was common to all of them. Based on findings with MCI and AD, they may not have had the sensitivity to detect subtle differences.

3.2.2.4 MCI Latency. Of the 29 studies that assessed P300 latency in MCI, 17 reported no significant group differences [i.e., 59%; 22,23,28-30,46,57,59,81,86,94,105,107,114,120,133,139]. All of the remaining studies (i.e., 41%) demonstrated delayed latency in MCI compared to HC groups [11-12,50-51,53,78,83,106,138,142,145,148]. Bennys and colleagues [12] further specified that P300 latencies in the progressive MCI group were more delayed than those of the non-progressive MCI and HC groups. Thus, P300 latency was more sensitive to neural differences in MCI than N200, even though most studies showing such differences used simple tasks (75% oddball tasks). However, it was notable that sample sizes in these studies were amongst the largest (e.g., 34 participants per group), perhaps allowing for greater sensitivity, even with a simple task.

3.2.2.5 AD Latency. Thirty articles analyzed P300 latency in AD. The majority reported delayed latency in AD compared to HC groups [i.e., 66%; 3,43,52,60,63,71,76,88,92,96-97,105,110-111,118,135,139,142,145,152], two of which reported non-significant trends [52,145]. No significant differences between groups were detected in eight studies [i.e., 27%; 4,31,47,69,75,84,114,126]. Two studies in fact reported shorter P300 latency in AD compared to HC groups [i.e., 7%; 13,72], although interpreting this in context of other studies is difficult because one also reported high P300 variability in the AD group [13], and the other used an atypically late window for the P300 component (i.e., 400-800ms) [72].

3.2.2.6 Cognitively Intact APOE ϵ 4 Carriers Latency. Three of five APOE studies reported delayed P300 latencies in the ϵ 4+ group when using an olfactory identification task [i.e., 60% of total studies; 93,95,147]. Notably, these same studies reported no group differences when using visual or auditory oddball paradigms in the same participants. The two remaining studies reported no significant differences [i.e., 40%; 39,54], using oddball paradigms and small samples (e.g., ten per cell).

3.2.3 N400

The N400 is a negative-going wave that peaks approximately 300-600ms after stimulus onset and is associated with the evaluation of meaningfulness, including semantic and language processing, and recognition memory [77]. This component can be elicited with various task paradigms. For example, N400 amplitude has an inverse relationship with semantic priming, in which novel stimuli tend to elicit larger amplitudes than primed stimuli [i.e., priming effect; 5,77]. Similarly, incongruent stimuli tend to elicit larger N400 amplitudes than congruent stimuli, a phenomenon often investigated by calculating difference waves [i.e., N400 congruity effect; 77,102]. Furthermore, N400 amplitude tends to decrease with repeated exposure to a stimulus [i.e., repetition effect; 102].

3.2.3.1 MCI Amplitude. Three of six studies that assessed N400 amplitude in MCI groups reported smaller amplitudes in MCI compared to healthy controls [i.e., 50%; 1,48,64]. Two of these studies used recognition memory paradigms [i.e., old/new effects; 1,64], while the third demonstrated a lack of visual object priming in MCI [48]. All three of these studies specifically assessed N400 amplitude at frontal electrodes (i.e., frontal N400, FN400), which has been suggested to index familiarity and conceptual implicit memory [32,80], with others suggesting

no functional distinction between N400 components with frontal vs. centro-parietal peaks [144]. A fourth study revealed larger N400 amplitudes in MCI vs. HC groups during a priming task. As amplitude should decrease to primed stimuli, this study indicated semantic priming deficits in the MCI group [i.e., 17%; 137], consistent with the other studies showing deficits in MCI vs. HC. The two final studies reported no significant group differences in N400 amplitude [i.e., 33%; 100,154] using word repetition and face recognition tasks. Thus, although few studies are yet available, N400 amplitude successfully differentiated between MCI and HC in 67% of studies.

3.2.3.1 AD Amplitude. The majority of AD studies showed smaller N400 amplitude in AD compared to HC groups across a variety of metrics, including smaller raw waveforms, priming, congruity, and repetition effects [i.e., 65%; 5,19,45,55,62,68,99,103,123,129,150]. Priming and repetition effects were the most frequently used approach; of the 11 studies demonstrating AD<HC, seven (i.e., 64%) used priming and/or congruency paradigms. The remainder used repetition, categorization, or word fluency tasks (see Table 2). In contrast, two studies reported larger amplitudes in AD compared to HC groups [i.e., 12%; 43,137]. Both were consistent with the other studies in showing priming deficits in AD. Ford and colleagues [43] reported this in context of larger N400 amplitudes to both primed and unprimed words in AD (typically primed<unprimed), while Taler et al. reported larger overall raw N400 amplitudes in AD compared to HC during semantic priming, although no differences between groups were apparent for semantic priming itself, and these samples were uneven in size and age distribution [137]. The final three AD studies reported no significant group differences in N400 amplitude [i.e., 24%; 42,71,126,137]. Two of these studies assessed N400 repetition effects

using a word recognition task with infrequent animal targets and had small sample sizes [71,126], while the other used picture-name congruity [42]. Although there is some inconsistency in this small literature, particularly with different tasks and methods of calculating N400 metrics, N400 amplitude nevertheless appears to differentiate between AD and HC more consistently (76%) than N200 (18%) and P300 (60%) amplitudes.

3.2.3.2 Cognitively Intact APOE ϵ 4 Carriers. Only one study with healthy, cognitively intact APOE groups examined the N400 component [74]. Carriers of the APOE ϵ 4 allele had greater N400 amplitude than non-carriers in the right hemisphere during an odor-image congruency task, which is typically a left-hemisphere dominant task. Midline N400 amplitudes, on the other hand, highlighted smaller amplitudes in the ϵ 4+ compared to ϵ 4- group. Consistent with MCI and AD studies, N400 amplitude discriminated between APOE groups more effectively than earlier (i.e., N200, P300) components.

3.2.3.3 MCI Latency. Only two studies assessed N400 latency with MCI groups. One reported prolonged latency in MCI compared to HC [100], while the other reported no significant group differences [154].

3.2.3.4 AD Latency. The majority of the nine studies that analyzed N400 latency reported significantly delayed latencies in AD groups compared to HC, including congruity effects, priming effects, and raw N400 latency [i.e., 66%; 19,42-43,68,99,129], with one reporting a non-significant trend [99]. The three remaining studies reported no significant difference between groups [i.e., 33%; 71,103,126], though it should be noted that each had very small samples (8-11 per cell). Notably, no studies to date have examined N400 latency in cognitively intact APOE ϵ 4 carriers.

3.2.4 Late Positive Component, Parietal Effect, & Late Positive Potential

The late positive component (LPC) is a positive-going wave that typically peaks around 500-800ms post-stimulus. The LPC is thought to reflect memory encoding and retrieval, especially for explicit recognition memory, and is often calculated as the difference between old and new trials (i.e., old/new effect). LPC also indexes semantic and syntactic processing, and may be investigated in a repetition paradigm similar to the N400 component [101,104]. The parietal effect (also ~500-800ms) is a recognition memory old/new effect (new>old) that is specifically largest over parietal electrodes [149]. Relatedly, the late positive potential (LPP) falls under these same parameters (e.g., new>old ~400-800ms) but is particularly evident during emotive tasks [61].

3.2.4.1 MCI Comparisons. Two of the three studies that investigated LPC amplitude reported smaller amplitudes in the MCI compared to HC groups [i.e., 67%; 16,100]. Both of these studies used repetition tasks, one an emotive image repetition with a working memory component [16] and the other a word repetition task [100]. The remaining study also reported smaller amplitudes in MCI compared to HC in the right hemisphere, but larger amplitudes in the left hemisphere during an olfactory oddball paradigm [i.e., 33%; 67]. This greater left hemisphere LPC magnitude was interpreted as a compensatory mechanism associated with deficits in earlier, sensory-level processing. The only study that assessed LPC latency did not find significant between-group differences [100]. With respect to the parietal effect in MCI, two of four studies reported no significant group differences [i.e., 50%; 48,64]. The other two reported smaller parietal effects in MCI compared to HC groups, one at a significant level [154], and the other only showing a non-significant trend [1]. Finally, all three studies that assessed

the LPP component reported significantly smaller LPP amplitudes in MCI compared to HC groups [16,116,146]. All three of these studies are very recent (i.e., 2016-2018), suggesting the need for future research with this component.

3.2.4.2 AD Comparisons. Of the six studies that investigated LPC amplitude in AD, three reported smaller amplitudes in AD groups compared to HC [i.e., 50%; 45,99,123], while the other three reported no significant group differences [i.e., 50%; 19,62,129]. Only one study thus far analyzed LPC latency, reporting no significant group differences [19]. There were no studies specific to the parietal effect or late positive potential with AD groups or any of these components in cognitively intact elders stratified by APOE ϵ 4.

3.2.5 Slow Waves

Slow wave ERPs follow the P300 component and are characterized by their slow onset, resembling plateaus rather than peaks. The specific role of slow wave potentials is still debated, but they are thought to generally reflect ongoing higher-order processing of stimuli [125]. No studies have been reported examining AD or ϵ 4 compared with controls, but four studies exist in MCI, which examined positive- and negative-slow waves during Go/No-go, auditory oddball, and task switching. Both studies that assessed slow wave amplitude reported larger amplitude in MCI compared to HC groups, including greater amplitude in single domain MCI compared to both multiple domain MCI and controls [30,131]. Furthermore, both studies of slow wave latency highlighted prolonged latency in MCI compared to HC [106-107].

4. Discussion

Overall, the literature examining cognitive ERPs in MCI, AD, or risk for AD (APOE ϵ 4) relative to HC is quite small. The 100 studies meeting criteria for this review predominantly

covered N200, P300 and N400, but they did so with mostly small samples and a wide range of approaches and sample characteristics. Yet, there is some consistency in findings across studies that lends confidence in the importance of cognitive ERPs toward assessment and early predictions of cognitive decline, as well as in directing future research. Here we endeavor to highlight those consistencies and directions.

4.1 N200

Given the frequency of oddball paradigms in the reviewed studies, the N200 component as we have covered it herein tends to index conscious, intentional attention to stimuli, especially to deviations from an expected stimulus [109]. Since attentional deficits are often evident in early stages of AD and may contribute to decline in other higher order cognitive processes, such as memory and planning [8,124], N200 is a candidate component to be sensitive to relatively subtle neural changes associated with AD. Despite this possibility, the majority of N200 amplitude studies detected no significant group differences (ϵ^4 : 100%; MCI: 67%; AD: 82%; see Table 5). However, conclusions from these studies are limited by an almost universal use of small, unbalanced samples (e.g., cells often ≤ 10) and simple, even passive, oddball paradigms. Indeed, during lesser-used higher-order cognitive tasks, such as executive attention or inhibitory control, or visual modality rather than auditory, N200 amplitude was significantly reduced in MCI and AD relative to HC. N200 in the context of executive functioning tasks may reflect conflict monitoring and pre-motoric alerting of the need to activate inhibitory control processes [56,66]. More research is needed to better understand the underlying processes associated with the N200 component with higher-order cognitive processes and to assess the discriminative ability of N200 in this context.

N200 latency discriminated between groups in approximately half of the studies ($\epsilon 4$: 100%; MCI: 47%; AD: 50%; see Table 5), despite the task and sample size limitations. Indeed, even in cognitively intact elders at risk for AD by carrying the APOE $\epsilon 4$ allele, prolonged N200 latency was apparent in all four studies regardless of task type and small samples. Moreover, follow-up testing in one of these studies demonstrated that N200 latency predicted verbal learning decline 3.5 years later [39]. Future investigation of the N200 component, particularly with visual or complex executive and attentional tasks, is important toward confirming whether the N200 is a robust index of early neural changes associated with pathological aging.

4.2 P300

The P300 component, which is associated with detection of novel stimuli, updating of working memory, inhibitory control, and selective attentional processes [109], may be sensitive to AD-related changes as deficits in working memory and attention are common in AD [7,10,49,132]. As such, P300 has been the most studied ERP component in this context. We note that despite different sources and cognitive processes associated with P300a vs. P300b, we were precluded from interpreting these distinctions because few of the studies specified P300 subcomponents. Thus, distinguishing these subcomponents is an important future direction.

Our review highlighted a diagnostic severity-indexed trend across studies of reduced P300 amplitude ($\epsilon 4$: 0%; MCI: 38%; AD: 60%; see Table 5) and prolonged latency ($\epsilon 4$: 60%; MCI: 41%; AD: 66%; see Table 5). P300 amplitude differences were best highlighted by executive function tasks, while P300 latency uniquely differentiated groups even during oddball paradigms when using larger samples. Thus, P300 latency was more robust to these group

differences than N200 latency in oddball tasks. Indeed, one P300 auditory oddball study further distinguished groups by severity of AD showing P300 amplitude was reduced late, in the moderate AD stage, while P300 latency was progressively delayed coincident with level of cognitive impairment, and evident earlier in the disease course than amplitude differences [60]. Although the literature in cognitively intact elders carrying APOE $\epsilon 4$ is very small with P300 (five studies), an olfactory identification task showed prolonged P300 latency in $\epsilon 4+$ that oddball tasks did not reveal. Olfactory tasks may be robust to group differences at various stages, though this modality requires specially built olfactometers and careful control over the sensory environment, which may limit their broad use.

Despite the relatively consistent pattern of reduced P300 amplitude and delayed P300 latency in well-powered AD studies, this pattern nevertheless was representative of only about 60-65% of the available studies. As such, conclusions about the sensitivity of P300 to early AD pathology should be made with caution. Notably, one study using a Stroop color-word interference task found delayed P300 latency in a middle-aged MCI group compared to middle-aged HC, with 0.9 sensitivity and specificity to distinguish the groups, suggesting that complex attention or executive tasks may be best able to characterize neural changes evident early in the course of neuropathology [120]. Thus, future research, particularly with complex attention and executive tasks assessing group differences in P300 amplitude, will be key to determining the value of P300 to early stage disease differences (e.g., APOE $\epsilon 4$ AD risk, MCI).

4.3 N400

The N400 component is associated with the evaluation of meaningfulness, including semantic and language processing, and recognition memory [77]. Deficits in multiple domains

of semantic and language processing are core features of AD progression [127,143]. Indeed, although episodic memory deficit is a hallmark of AD, semantic memory impairment is estimated to affect at least 50-82% of those with AD [143]. While less commonly investigated, there is also evidence of semantic deficits in MCI [38,70]. Thus, the N400 may be an important candidate for indexing early neural changes associated with AD. Consistent with this contention, N400 amplitude most consistently differentiated MCI (67%) and AD (76%) from HC groups across the components we reviewed (see Table 5). Amplitudes were generally smaller in MCI and AD compared to HC using raw waveforms, priming, congruity, and repetition effects, accompanied by evidence of reduced or absent priming and repetition effects in MCI and AD. These consistent patterns across various approaches highlight the disruption of semantic networks evident with AD pathology. Furthermore, MCI studies particularly highlighted the importance of the frontal N400 [i.e., FN400, early frontal effect; 144], which is thought to index familiarity and arguably identical in source to the traditional N400 [but also see 15]. Importantly, during recognition memory paradigms, it both distinguished MCI from HC group and correlated with episodic memory performance and medial temporal lobe gray matter volume [64].

Despite these promising findings, research with the N400 is lacking, particularly in MCI, compared with other components; only 6 MCI studies exist (see Tables 2 & 5). Even less well studied is N400 latency, despite the generally strong indication that it is prolonged in AD (67%; see Table 5). Moreover, only one study analyzed N400 amplitude with cognitively intact APOE $\epsilon 4$ carriers, revealing right hemisphere recruitment during a left hemisphere task, thereby suggesting a compensatory function [18,108,122]. This was the only available study of AD risk

groups that examined a later cognitive ERP component or used a more complex cognitive task. Indeed, it was also the only study to reveal significant differences in ERP amplitude between cognitively intact AD risk groups, despite having only ten participants per group. Thus, the N400 component demonstrates promise for distinguishing between healthy and pathological aging. Future N400 research using complex cognitive tasks with MCI, AD, and healthy AD risk groups is critical to improve understanding of early changes that presage cognitive decline.

4.4 Other late components and non-traditional approaches

While little investigated, other later components reflective of recognition memory show promise for discriminating MCI (LPC, PE, and LPP) and AD (LPC) from healthy control groups, generally showing reduced amplitude in MCI and AD (see Table 5). No studies have yet investigated latency for these components between these groups. Similarly, slow waves, which may reflect cognitive processes such as memory or emotion processing depending on the context, have been little studied in MCI and AD, but the two existing studies showed smaller amplitude and delayed latency in MCI relative to HC across both low-level and complex tasks (see Table 5). Future research on these components is particularly important given promising results in so few studies that varied greatly in task and study characteristics. As noted based on components that have received more study than these, additional studies using complex tasks might be particularly effective at discriminating between groups, perhaps especially at an early stage preceding measurable cognitive impairment.

4.5 Conclusions and Future Directions

The existing literature in MCI, AD, and APOE $\epsilon 4$ risk for AD suggests more research is warranted investigating cognitive ERPs as potential biomarkers of AD-related neuropathology.

The studies reviewed highlight overall patterns of reduced amplitude and delayed latency in pathological aging (MCI, AD) compared to healthy controls, particularly in advanced disease progression and when examining later ERP components with relatively complex cognitive tasks. Such patterns are particularly evident in AD, where reduced P300 and N400 amplitude and prolonged N200, P300, and N400 latency were common findings. Similar but less robust patterns were evident in MCI. Strikingly, only six studies examining cognitively intact participants with risk for AD met inclusion criteria for this review, four of which used olfactory ERPs. They typically showed prolonged ERP latencies in $\epsilon 4$ carriers relative to non-carriers, while only one differentiated ERP amplitude by AD risk; using a late component (N400) and a complex task with relevant lateral electrodes, increased right hemisphere amplitude suggested compensatory activation in $\epsilon 4$ carriers [74]. This finding was consistent with recent fMRI research showing initially greater neural activation in cognitively intact older adults who carry the APOE $\epsilon 4$ allele [14,121,151], which reverses over time in $\epsilon 4$ carriers who exhibit cognitive decline, compared with a steady increase in activation in non-carriers [121].

Our review also highlighted the gaps in this scant literature, including the small number of existing studies, small samples, vastly varying paradigms and analytical methods, lack of subcomponent differentiation and lateral electrode analysis, and variability in age and cognitive functioning in comparison groups. Indeed, such differences, and an overall paucity of reporting of key contrast data or effect sizes substantively deter meaningful and reproducible meta-analyses within and across components. Yet, these limitations did not preclude the ability to see overall patterns hinting at promise for ERPs as a feasible approach to an early index of AD. Future studies that specifically examine later cognitive ERP components in AD, MCI and

cognitively intact AD-risk with larger, comparable groups and preferably complex cognitive tasks are urgently needed to evaluate that promise. Future research must also aim to establish the sensitivity and specificity of ERPs in differentiating between groups. This would allow determination of whether ERPs could be useful in combination with neuropsychological testing toward identification, prediction, and tracking of neural changes prior to and coinciding with cognitive decline, thereby assisting with targeting for intervention.

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Table 1.
Results of MCI Studies Included in the Review.

Authors (Year)	ERP Task(s)	ERP Component(s)	Electrodes	Amplitude Effects	Latency Effects	Reference (text)
Ally et al. (2009)	Recognition memory	N400 ¹ , PE, LFE	ROIs (7 site avg): LAI, RAI, LAS, RAS, LPS, RPS, LPI, RPI	N400 ¹ (LAI, LAS, RAS): MCI<HC; PE (LPS): MCI<HC (tr); LFE: MCI>HC _p (LAI, LAS), MCI<HC _w (RAS)	--	1
Bennys et al. (2011)	Auditory oddball	N200; P300	Fz, Pz	N200 (Pz): MCI ^a <MCI ^b , HC; P300 (Pz): MCI ^a <MCI ^b , HC	N200 (Fz, Pz): MCI ^a >HC; P300 (Pz): MCI ^a >MCI ^b , HC	12
Bennys et al. (2007)	Auditory oddball	N200; P300	Fz, Pz	NS	N200 (Fz, Pz): MCI>HC; P300 (Fz, Pz): MCI>HC	11
Broster et al. (2018)	Emotive images, WM (DMS)	LPP; LPC	Peak site, each PCA	LPP (Fz, Pz): MCI<HC; LPC (Fz, Pz): MCI<HC	--	16
Cespon et al. (2013)	Simon	N2pc	PO7, PO8 (DW)	MCI<HC	NS	20
Cespon et al. (2015a)	Simon	N2pc; N2cc	N2pc: PO7, PO8 (DW); N2cc: C3, C4 (DW)	N2pc: MCI ^d <HC; N2cc: NS	N2pc: NS; N2cc: MCI ^d > HC	21
Cespon et al. (2015b)	Simon	N200; N2pc; P300	N200, P300: Fz, Cz, Pz, Oz; N2pc: PO7, PO8 (DW)	N200: NS; N2pc: MCI ^d <HC; P300: NS	N200 (Pz): MCI ^d >HC; N2pc: NS; P300: NS	22
Chan et al. (2013)	Visual tool-using gesture	P300	FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2	MCI<HC (F4, P3, Pz, T5, T6)	NS	23

Chiang et al. (2015)	Semantic retrieval	Left fronto-temporal effect; fronto-parietal effect	62 sites (PCA)	Left fronto-temporal: NS; Fronto-parietal (FP1, F3, Pz, P2): MCI>HC	--	27
Chiang et al. (2018)	Semantic go/no-go	N200; P300	N200: Fz, FCz, Cz (avg); P300: FCz, Cz, Pz (avg)	NS	N200: MCI>HC (tr)	28
Cid-Fernández et al. (2014)	Go/no-go	N200; P300	Cz, Pz	N200 (Cz): MCI<HC; P300: NS	NS	29
Cid-Fernández et al. (2017)	Go/no-go	N200; P300; PSW	Fz, Cz, Pz	N200 [^] : Go MCI ^c <HC; No-go MCI ^c , MCI ^d <HC; P300: NS; PSW (Cz, Pz): MCI ^c >MCI ^d , HC	N200 [^] : Go MCI ^d >HC; P300: NS; PSW: --	30
Deiber et al. (2011)	Face/letter DMS	N250r	FC4, C4, CP4	MCI ^d <HC (C4, CP4)	NS	36
Fraga et al. (2018)	N-back	P450	--	MCI<HC (P4)	--	44
Frodal et al. (2002)	Auditory oddball	P300	F3, F4, P3, P4	NS	NS	46
Galli et al. (2010)	Identification-priming	N400 ¹ , PE	F7, Fz, F8, FT7, FCz, FT8, T3, Cz, T4, T5, Pz, T6	N400 ¹ (left fronto-central): MCI<HC; PE: NS	--	48
Golob et al. (2007)	Auditory oddball	P300	Pz	--	MCI ^c >HC (Pz)	50
Golob et al. (2002)	Auditory oddball	N200; P300	N200: Cz, P300: Pz	NS	N200: NS; P300 (Pz): MCI>HC	51
Gozke et al. (2016)	Visual oddball	N200; P300	Fz, Cz, Pz	N200: NS; P300 [^] : MCI<HC	N200 [^] : MCI>HC; P300 [^] : MCI>HC	53

Gu et al. (2017)	N-back	P300	CP1, CPz, CP2, P1, Pz, P2	MCI<HC (CPz, CP2, P1, P2)	NS	59
Gu et al. (2018)	N-back	P300	CP1, CPz, CP2, P1, Pz, P2	MCI<HC (CP2, P1, Pz, P2)	NS	57
Hoppstadter et al. (2013)	Recognition memory	N400 ¹ , PE	ROIs (6 site avg): RH, LH; anterior, posterior	N400 ¹ (anterior RH): MCI<HC; PE: NS	--	64
Invitto et al. (2018)	Olfactory oddball	LPC	Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, Pz, P7, P8, O1, O2, F7, F8	MCI>HC (F7(LH)); MCI<HC (F8(RH))	--	67
Lai et al. (2010)	Auditory oddball	N200; P300	Fz, Cz, Pz	NS	N200: NS; P300 (Pz @ baseline, Cz, Pz @ follow-up) MCI>HC	78
Li et al. (2016)	DMS	N200; P300	N200: F3, Fz, F4, FCz, C3, Cz, C4; P300: O1, O2, Pz	N200: NS; P300 [^] : MCI<HC	NS	81
Li et al. (2010)	Auditory oddball	N200; P300	N200: Cz; P300: Pz	N200: NS; P300 (Pz): MCI<HC	N200: NS; P300 (Pz): MCI>HC	83
Li et al. (2017)	WM (DMS)	P300	F3, F5, F7, F4, F6, F8	MCI>HC (LH)	--	82
Lopez Zunini et al. (2016)	Go/no-go	N200; P300	Fz, FCz, Cz, CPz, Pz	N200: NS; P300 (all): MCI<HC	NS	86
Missonnier et al. (2007)	N-back	N200	F3, Fz, F4, C3, Cz, C4	--	[^] MCI ^a >MCI ^b ,HC	90
Mudar et al. (2015)	Semantic go/no-go	N200; P300	N200: Fz, FCz, Cz (avg); P300: FCz, Cz, Pz (avg)	NS	N200: MCI>HC; P300: NS	94

Olichney et al. (2002)	Word repetition	N400; LPC	F7, F8, Cz, T5, T6, O1, O2; ROIs	N400: NS; LPC^: MCI<HC	N400^: MCI>HC; LPC: NS	100
Papadaniil et al. (2016)	Auditory oddball	P300	Pz	NS	NS	105
Papaliagkas et al. (2008)	Auditory oddball	N200; P300; slow wave	Cz, Pz	N200^: MCI>HC; P300: NS; SW: --	N200: NS; P300^: MCI>HC; SW^: MCI>HC	106
Papaliagkas et al. (2011)	Auditory oddball	N200; P300; slow wave	Cz, Pz	N200^: MCI>HC; P300: NS; SW: --	N200^: MCI>HC; P300: NS; SW^: MCI>HC	107
Phillips et al. (2004)	Sternberg	P300	Pz	NS	NS	114
Pietto et al. (2016)	Visual short-term memory	LPP	Left, Right, and FC, CP, PO (avg)	MCI<HC (right FC, CP; left/right avg CP)	--	116
Ramos-Goicoa et al. (2016)	Stroop	N200; P300	N200: AFz, Fz, Cz; P300: Fz, Cz, Pz	N200: NS; P300 (Pz): MCI>HC	NS	120
Sinai et al. (2010)	Task switching	"Switch cost" negative slow wave	FPz, Fz, FCz, Cz, CPz, Pz	MCI>HC^	--	131
Stothart et al. (2015)	Visual oddball	P300	Occipital ROI O1, Oz, O2, PO9, P10, PO7, PO8 (avg)	NS	NS	133
Taler et al. (2009)	Semantic priming	N400	Fz, FCz, Cz, CPz, Pz; 4-site LH-RH avg	MCI>HC (Pz)	--	137
Tsai et al. (2016)	Task-switching	P300	Fz, Cz, Pz	MCI<HC^	MCI>HC^	138

Tsolaki et al. (2017)	Two-tone auditory oddball	P300	Pz	NS	NS	139
van Deursen et al. (2009)	CNV paradigm; auditory oddball	CNV; N200; P300	Fz, Cz, Pz	NS	CNV: --; N200: NS; P300 (Pz): MCI>HC	142
Wang et al. (2013)	Flanker	N200; P300	N200: F3, Fz, F4 (avg); P300: P3, Pz, P4 (avg)	N200: MCI<HC; P300: MCI<HC	N200: MCI>HC; P300: MCI>HC	145
Waninger et al. (2018)	Vigilance; image recognition	LPP	Fz, F3, F4, Cz, C3, C4, P3, P4, Pz, O1, O2, T5, T3, F7, F _p 1, F _p 2, F8, T4, T6, POz	MCI<HC (all)	--	146
White et al. (2018)	Letter-face paradigm	P300	Cz, Pz	MCI<HC (Cz, Pz)	MCI>HC (Pz)	148
Yang et al. (2015)	Face recognition	N400 ¹ , PE	Avg; F (F5, Fz, F6), C (C5, Cz, C6), P (P5, Pz, P6), O (CB1, Oz, CB2)	N400 ¹ : NS; PE (central, parietal): MCI<HC	N400 ¹ : NS; PE: --	154

Notes: MCI = Mild Cognitive Impairment; HC = older adult controls; A = amplitude; L = latency; LH = left hemisphere; RH = right hemisphere; DW = difference wave; ROI = region of interest; PCA = principal components analysis; WM = working memory; -- = data not available/reported; avg = average(s); tr = non-significant trend; _p = pictures; _w = words; ^site(s) not specified; ^apMCI = progressing MCI; ^bnpMCI = non-progressing (stable) MCI; ^csdMC = single-domain (amnesic) MCI; ^dmdaMCI = multi-domain amnesic MCI; ^emdnaMCI = multi-domain non-amnesic MCI; ^faMCI = amnesic MCI; DMS = delayed match-to-sample; NS = not significant; -- = not investigated/reported; EFE¹=early frontal effect (frontal N400); PE=parietal effect; LFE=late frontal effect (>1000ms); LPP=late positive potential; LPC=late positive component; (P)SW=(positive) slow wave; CNV=contingent negative variation; LAI/RAI = left/right anterior inferior ROI; LAS/RAS = left/right anterior superior ROI; LPS/RPS = left/right posterior superior ROI; LPI/RPI = left/right posterior inferior ROI; *Cohen's d, absolute value--estimated where necessary.

Table 2.

Results of AD, Apolipoprotein-E $\epsilon 4$ Studies Included in the Review.

Authors (Year)	ERP Task(s)	ERP Component	Electrodes	Amplitude Effects	Latency Effects	Reference (text)
Asaumi et al. (2014)	Visual oddball	P300	Fz, Cz, Pz, Oz	AD<HC (all)	AD>HC (all)	3
Ashford et al. (2011)	Auditory oddball	P300	Pz	AD<HC (Pz)	NS	4
Auchterlonie, Phillips, & Chertkow (2002)	Word-picture semantic priming	N400	P3, Pz, P4	AD<HC [^]	--	5
Boller et al. (2002)	Auditory discrimination	P300	--	AD<HC	AD<HC	13
Castañeda et al. (1997)	Pictorial semantic categorization	N400, LPC	Fz, Cz, Pz, PC3, CP3, T3, TP7, FC4, CP4, T4, TP8	N400 (all): AD<HC; LPC: NS	N400 (all): AD>HC; LPC: NS	19
Chapman, et al. (2016)	Number-letter working memory	C250	2-3 site avg: frontal, central, parietal, occipital	NS	--	24
Cheng & Pai (2010)	Familiar, novel face & scene discrimination	N250r	FP1, FP2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FT7, FT8, Cz, C3, C4, T7, T8, CPz, CP3, CP4, TP7, TP8, Pz, P3, P4, P7, P8, Oz, O1, O2	AD>HC (F3)	NS	26
Cintra et al. (2017)	Auditory oddball	N200, P300	Fz	NS	NS	31
Espeseth et al. (2009)	Auditory oddball	N200, P300	Fz, Cz, Pz	NS	N200 [^] : $\epsilon 4/\epsilon 4 > \epsilon 3/\epsilon 4$; P300: NS	39
Ford et al. (2001)	Picture-name congruity	P300, N300, N400	3-site avg: F3, Fz, F4 (frontal); C3, Cz, C4 (central); P3, Pz, P4 (parietal)	P300 [^] : AD<HC (tr); N300: NS; N400: NS	P300: --; N300: NS; N400 [^] : AD>HC	42

Ford et al. (1996)	Auditory oddball; Semantic, phonemic monitoring	P300, N400	Fz,Cz,Pz; 3-site avg: F3, Fz, F4 (frontal); C3, Cz, C4 (central); P3, Pz, P4 (parietal)	P300 [^] : AD<HC; N400 [^] : AD>HC	AD>HC (Pz)	43
Friedman et al. (1992)	Word-repetition priming	N400, LPC	Fz, Cz, Pz, O1, O2	AD<HC (Fz)	--	45
Gaeta et al. (1999)	Passive auditory	P300	Cz	NS	NS	47
Gordon et al. (1989)	Auditory discrimination	P300	Fz, Cz, Pz	--	AD>HC (trend, Fz)	52
Green & Levey (1999)	Auditory oddball	N200, P300	Fz, Cz, Pz	NS	N200 (all): $\epsilon_4+>\epsilon_4-$ P300: NS	54
Grieder et al. (2013)	Semantic priming	N400	Topographic component analysis; all electrodes	AD<HC [^]	--	55
Gungor et al. (2005)	Auditory oddball	N200, P300	Fz, Cz	N200: NS; P300 (Fz, Cz): Mod<Mild=HC	N200: NS; P300 (Fz, Cz): Mod>Mild>HC	60
Hamberger et al. (1995)	Semantic priming terminal word decision	N400, LPC	F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T5, T6, O1, O2	N400 [^] : AD<HC LPC: NS	--	62
Hirata et al. (2000)	Auditory oddball	N200, P300	Global field power: Fp1 ,Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, T5, T6, O1, Oz, O2	N200: NS; P300 [^] : AD<HC	N200 [^] : AD<HC; P300 [^] : AD>HC	63
Iragui, Kutas, & Salmon (1996)	Word pair congruity	N400	F7, F8, Cz, T5, T6, O1, O2; +ROIs	AD<HC [^]	AD>HC [^]	68
Jacob & Duffy (2014)	Word and motion flow decision	N200, P300	O1, Oz, O2, Pz	NS	NS	69
Kazmerski & Friedman (1997)	Verbal category recognition	P300, N400	Fz, Cz, Pz	P300 (Cz, Pz): AD<HC; N400: NS	P300 (Cz, Pz): AD>HC; N400: NS	71

Kazmerski, Friedman, & Hewitt (1995)	Semantic repetitions	P300	Fz, Cz, Pz	NS	AD<HC (Pz)	72
Kazmerski, Friedman, & Ritter (1997)	Auditory oddball	N200, P300	Fz, Cz, Pz	NS	--	73
Kowalewski & Murphy (2012)	Odor-image congruency	N400	12 ROIs/condition (6-7 site avg): left/right, anterior/posterior, dorsal/ventral, and individual midline	$\epsilon_4+>\epsilon_4-$ (RH dorsal, ventral); $\epsilon_4+<\epsilon_4-$ (Pz)	--	74
Kraiuhin et al. (1990)	Two-tone auditory discrimination	P300	Fz, Cz, Pz	--	NS	75
Kraiuhin et al. (1989)	Two-tone auditory discrimination	P300	Fz, Cz, Pz	--	AD>HC (Fz)	76
Lockwood, Vaughn, & Duffy (2018)	Attentionally cued orientation discrimination	N200, N2pc, P300, CNV	Avg: CP3, P3, T5 (LH); CP4, P4, T6 (RH)	N200, N2pc, P300 [^] : AD<HC; CNV: NS	NS	84
Marsh et al. (1990)	Auditory target tone	P300	Pz	--	AD>HC (Pz)	88
Mathalon et al. (2003)	Picture-name verification	P300	Fz, Cz, Pz	P300 [^] : AD<HC	--	89
Morgan & Murphy (2002)	Single stimulus (auditory, olfactory)	N200, P300	Fz, Cz, Pz	NS	N200 [^] : AD>HC; P300 [^] : AD>HC	92
Morgan & Murphy (2012)	Visual, olfactory identification	N200, P300	Fz, Cz, Pz	NS	N200 [^] : $\epsilon_4+>\epsilon_4-$; P300 [^] : $\epsilon_4+>\epsilon_4-$	93
Murphy et al. (2009)	Odor recognition	P300	Fz, Cz, Pz	--	$\epsilon_4+>\epsilon_4-$ [^]	95
O'Mahony et al. (1996)	Auditory target tone	N200, P300	Fz, Cz, Pz	--	AD>HC [^]	96

O'Mahony et al. (1993)	Auditory target tone	P300	Fz, Pz	--	AD>HC (Fz)	97
Olichney et al. (2006)	Semantic repetition congruity	N400, LPC	Fz, F7, F8, Cz, Pz, T5, T6, O1, O2; ROI's	AD<HC^	N400^: AD>HC (tr); LPC: --	99
Ostrosky-Solis et al. (1998)	Picture congruity matching	N400	Fz, Cz, Pz, Oz, FC3, CP3, T3, TP7, FC4, CP4, T4, TP8	AD<HC (all)	NS	103
Papadaniil et al. (2016)	Auditory oddball	P300	Pz	NS	AD>HC (Pz)	105
Patterson, Michalewski, & Starr (1988)	Auditory oddball	N200, P300	Fz, Cz, Pz	NS	AD>HC^	110
Pedroso et al. (2018)	Auditory oddball	P300	Fz	--	AD>HC (Fz)	111
Phillips et al. (2004)	Sternberg working memory	P300	Pz	AD<HC (Pz)	NS	114
Polich, Ladish, & Bloom (1990)	Target-tone auditory discrimination	N200, P300	Fz, Cz, Pz	N200: NS; P300^: AD<HC	AD>HC^	118
Revonsuo et al. (1998)	Semantic priming congruity	N400, LPC	FP1, FP2, F7, F8, F3, F4, Fz, T3, T4, C3, C4, Cz, T5, T6, P3, P4, Pz, O1, O2, Oz	AD<HC^	--	123
Rugg et al. (1994)	Word repetition, infrequent targets	P300; N400	Fz, Cz, Pz,, 50% distance from: F3:F7, F4:F8, C3:T3, C4:T4, P3:T5, P4:T6	NS	NS	126
Schwartz et al. (1996)	Categorical semantic priming	N400, LPC	Fz, F7, F8, Cz, Pz, T5, T6, O1, O2; ROIs	N400^: AD<HC; LPC: NS	N400^: AD>HC; LPC: --	129
Sumi et al. (2000)	Auditory oddball	N200, P300	Pz	--	AD>HC (Pz)	135
Taler, Klepousniotou, & Phillips (2009)	Semantic priming	N400	Fz, FCz, Cz, CPz, Pz	Raw (CPz, Pz): AD>HC; Priming: NS	--	137

Tsolaki et al. (2017)	Two-tone auditory oddball	P300	Pz	NS	AD>HC (Pz)	139
van Deursen et al. (2009)	Auditory target tone oddball; CNV paradigm	N200, P300, CNV	Fz, Cz, Pz	N200,CNV: NS P300 (Cz, Pz): AD<HC	N200: NS; P300 (Fz, Cz): AD>HC	142
Wang et al. (2013)	Eriksen flanker	N200, P300	N200: F3, Fz, F4; P300: P3, Pz, P4	AD<HC^	AD>HC (tr)^	145
Wetter & Murphy (2001)	Auditory, olfactory identification	N200, P300	Fz, Cz, Pz	NS	$\epsilon_4 > \epsilon_4^-$	147
Wolk et al. (2005)	Recognition, conceptual fluency	N400, LFE	N400: FPz, Fz, Cz, Pz, Oz; LFE: FPz, Fz	N400^: AD<HC; LFE^: AD<HC (trend)	--	150
Yamaguchi et al. (2000)	Auditory oddball	P300	Fz, Cz, Pz	AD<HC (all)	AD>HC (all)	152

Notes: AD = Alzheimer's disease; FH = family history of AD; HC = older adult controls; A = amplitude; L = latency; LH = left hemisphere; RH = right hemisphere; Mod = moderate; NS = not significant; -- = data not available/reported; ^site(s) not specified; avg = average(s); tr = non-significant trend PE=parietal effect; LFE=late frontal effect (>1000ms); LPC=late positive potential; CNV=contingent negative variation.

Table 3.

Demographic Data (mean (SD) or range, as reported) MCI Studies Included in the Review.

Authors (Year)	Total N^a	MCI N	HC N	MCI Age	HC Age	MCI MMSE	HC MMSE	Reference (text)
Ally et al. (2009)	36	18	18	71.8 (9.2)	74.6 (4.1)	28.1 (1.3)	29.4 (0.8)	1
Bennys et al. (2011)	102	71	31	70.7 (9.0) ^a 72.0 (7.8) ^b	71.2 (9.2)	25.4(3.2) ^a 26.4 (2.7) ^b	29.5 (0.6)	12
Bennys et al. (2007)	60	20	10	64.4 (7.6)	61.6 (6.4)	27.0 (1.6)	29.6 (0.5)	11
Broster et al. (2018)	32	16	16	77.2 (1.5)	76.7 (1.4)	26.2 (0.7)	28.8 (0.3)	16
Cespon et al. (2013)	55	30	25	67.0 (9.1) ^c 71.0 (9.2) ^d	65.2 (8.2)	27.2 (1.9) ^c 23.5 (1.7) ^d	28.4 (1.3)	20
Cespon et al. (2015a)	43	25	18	69.1 (2.0) ^c 71.2 (2.1) ^d	68.3 (1.7)	26.9 (0.5) ^c 23.7 (0.5) ^d	28.5 (0.4)	21
Cespon et al. (2015b)	53	38	15	66.5 (9.7) ^e 67.1 (9.3) ^c 69.6 (9.0) ^d	66.0 (7.5)	24.4 (2.4) ^e 27.2 (1.9) ^c 23.7 (1.6) ^d	28.3 (1.2)	22
Chan et al. (2013)	50	17	17	70.7 (7.9)	67.9 (6.7)	23.2 (5.1)	28.3 (1.6)	23
Chiang et al. (2015)	33	16	17	69.7 (7.9)	64.9 (6.6)	28.3 (1.3)	28.4 (0.9)	27
Chiang et al. (2018)	50	25	25	68.5 (8.0)	65.4 (7.1)	--	--	28
Cid-Fernández et al. (2014)	93	30	63	69.5 (8.2)	65.9 (8.0)	25.9 (2.4)	28.2 (1.5)	29
Cid-Cernández et al. (2017)	54	34	20	68.7 (10.1) ^c 72.1 (6.9) ^d	67.0 (9.8)	26.9 (2.0) ^c 23.4 (1.7) ^d	28.0 (1.5)	39
Deiber et al. (2011)	79	43	36	65.8 (5.4) ^c 64.0 (5.3) ^d	64.7 (6.6)	28.2 (1.5) ^c 27.7 (1.9) ^d	29.0 (0.8)	36
Fraga et al. (2018)	63	21	27	79.9 (1.1)	77.6 (1.0)	--	--	44
Frodil et al. (2002)	82	26	26	66.2 (11.3)	64.9 (10.9)	27.5 (1.6)	29.7 (0.5)	46
Galli et al. (2010)	32	17	15	73.1 (4.9)	70.4 (5.7)	25.5 (3.4)	28.9 (0.8)	48

Golob et al. (2007)	134	41	44	74.6 (5.9) ^c 76.0 (5.2) ^d	75.1 (5.7)	27.4 (1.6) ^c 27.4 (2.4) ^d	29.0 (1.1)	50
Golob et al. (2002)	23	15	12	76.5 (2.7)	72.8 (7.8)	27.7 (1.9)	29.2 (0.8)	51
Gozke et al. (2016)	40	20	20	66.0 (3.6)	66.3 (4.4)	--	--	53
Gu et al. (2017)	82	39	43	71.2 (5.4) ^g 71.3 (6.3) ^h	70.2 (5.3) ^g 70.2 (5.7) ^h	26.9 (2.6) ^g 27.2 (1.9) ^h	28.1 (1.6) ^g 28.7 (1.1) ^h	59
Gu et al. (2018)	85	39	46	71.3 (6.0)	70.2 (5.6)	27.1 (2.1)	28.4 (1.3)	57
Hoppstadter et al. (2013)	24	14	10	68.0 (4.0)	67.8 (4.7)	27.9 (1.3)	28.9 (1.1)	64
Invitto et al. (2018)	24	12	12	70.3 (7.7)	66.4 (5.7)	--	--	67
Lai et al. (2010)	32	18	14	68.0 (8.7)	64.8 (7.8)	23.1 (0.8)	28.3 (1.5)	78
Li et al. (2016)	46	24	22	69.3 (7.6)	69.2 (8.9)	26.4 (2.1)	29.0 (1.0)	81
Li et al. (2010a)	68	34	34	72.5 (5.4)	71.6 (5.7)	24.4 (3.8)	28.1 (1.5)	83
Li et al. (2017)	48	17	18	75.3 (9.2)	75.1 (5.0)	27.8 (1.8)	29.3 (0.8)	82
Lopez Zunini et al. (2016)	32	15	17	75.6 (6.0)	72.8 (5.9)	--	--	86
Missonier et al. (2007)	55	29	16	82.1 (5.3) ^a 82.0 (9.0) ^b	71.6 (9.0)	25.5 (1.8) ^a 26.7 (1.9) ^b	28.6 (1.2)	90
Mudar et al. (2015)	50	25	25	68.5 (8.0)	65.4 (7.1)	28.4 (1.3)	28.6 (0.5)	94
Olichney et al. (2002)	28	14	14	74.6	74.0	27.0 (1.7)	--	100
Papadaniil et al. (2016)	63	21	21	72.0 (4.7)	67.0 (2.7)	27.0 (1.4)	28.8 (0.9)	105
Papaliagkas et al. (2008)	121	91	30	66.6 (5.4)	68.9 (9.9)	27.7	29.7	106
Papaliagkas et al. (2011)	52	22	30	67.4 (7.8)	--	27.9 (1.9)	--	107
Phillips et al. (2004)	45	15	16	75.8 (6.4)	75.2 (5.5)	27.6 (2.1)	28.8 (1.2)	114
Pietto et al. (2016)	47	23	24	73.1 (9.0) 44.4 (3.2)	67.2 (10.1) 44.3 (5.6)	26.5 (2.5) 25.2 (4.5)	29.5 (0.5) 29.1 (1.1)	116

Ramos-Goicoa et al. (2016)	84	39	45	70.7 (9.1)	65.4 (9.2)	25.5 (2.5)	28.5 (1.3)	120
Sinai et al. (2010)	46	27	19	75.5 (1.7) ^j 77.0 (2.9) ^k 76.5 (2.6) ^l	75.7 (1.5)	28.4 (0.4) ^j 26.2 (0.8) ^k 25.2 (0.8) ^l	28.6 (0.4)	131
Stothart et al. (2015)	71	25	26	77.3 (7.4)	76.0 (7.0)	25.9 (1.9)	28.5 (1.2)	133
Taler et al. (2009)	49	20	19	75.8 (7.6)	74.7 (7.6)	27.4 (2.3)	--	137
Tsai et al. (2016)	60	30	30	68.2 (5.3)	66.9 (4.4)	27.6 (2.0)	28.6 (1.2)	138
Tsolaki et al. (2017)	63	21	21	72.0 (4.7)	67.0 (2.7)	27.0 (1.4)	28.8 (0.9)	139
van Deursen et al. (2009)	55	20	20	70.6 (7.2)	69.5 (6.1)	26.3 (1.6)	29.3 (0.8)	142
Wang et al. (2013)	38	15	16	72.9 (1.9)	69.3 (1.8)	27.0 (0.5)	29.3 (0.5)	145
Waninger et al. (2018)	~35	18	17	69.0 (0.4)	67.3 (1.6)	27.9 (0.5)	29.2 (0.2)	146
White et al. (2018)	11	5	6	--	--	--	--	148
Yang et al. (2015)	48	24	24	71.5 (4.5)	71.8 (3.7)	26.6 (1.9)	28.8 (1.4)	154

Notes: MCI = Mild Cognitive Impairment; HC = older adults (controls); -- = data not available/reported; ^sample size included in analyses; Mod=moderate; ^aprogressing MCI; ^bnon-progressing (stable) MCI; ^csingle-domain (amnestic) MCI; ^dmulti-domain amnestic MCI; ^emulti-domain non-amnestic MCI; ^famnestic MCI; ^gε4+; ^hε4-; ⁱfamilial AD; ^jMCI-able; ^kMCI-cue; ^lMCI-unable; ~all participants consulted memory disorder clinic; †included 3 participants with cardiovascular (multi-infarct) dementia; ‡AD group included individuals with neuropsychological memory deficits with no known cause or probable AD.

Table 4.

Demographic Data (mean (SD) or range, as reported) AD, APOE Studies Included in the Review.

Authors (Year)	Total N ^a	AD N	HC N	AD Age	HC Age	AD MMSE	HC MMSE	Reference (text)
Asaumi et al. (2014)	~48	36	12	74.1 (7.2)	71.0 (5.9)	20.7 (3.1)	28.8 (0.9)	3
Ashford et al. (2011)	48	23	11	63-93	61-80	16.6 (7.3)	28.8 (1.7)	4
Auchterlonie et al. (2002)	24	9	15	79.3 (4.2)	70.7 (5.7)	--	--	5
Boller et al. (2002)	22	10	12	75 (8.1)	75 (6.2)	19.6 (2.9)	28.8 (1.2)	13
Castañeda et al. (1997)	20	10	10	59-89	54-82	--	--	19
Chapman, et al. (2016)	108	36	36	74.9 (7.4)	74.2 (7.1)	24.6 (2.7)	29.1 (0.9)	24
Cheng & Pai (2010)	37	20	17	71.1 (8.2)	69.5 (9.6)	21.8 (3.4)	28.4 (1.7)	26
Cintra et al. (2017)	65	17	14	76.3 (7.9)	74.5 (9.3)	--	--	31
Espeseth et al. (2009)	41	--	20 ^a 13 ^b 8 ^c	--	63.4(8.7) ^a 62.9(8.7) ^b 60.5(9.7) ^c	--	--	39
Ford et al. (2001)	39	13	13	74.5 (8.2)	73.8 (5.7)	20.5 (2.7)	29.8 (0.4)	42
Ford et al. (1996)	36	12	12	57-82	58-76	20.3 (3.6)	28.2 (1.3)	43
Friedman et al. (1992)	30	10	10	70.6 (9.2)	69.8 (6.3)	--	--	45
Gaeta et al. (1999)	16	8	8	72.5 (7.5)	72.8 (6.5)	--	--	47
Gordon et al. (1989)	39	8	31	81.0 (7.8)	71.0 (4.1)	--	--	52
Green & Levey (1999)	40	--	23 ^f 9 ^{dg} 8 ^{eg}	--	55.4 (4.4) ^f 55.5(5.0) ^g	--	--	54
Grieder et al. (2013)	38	14	19	66.5 (9.6)	69.5 (3.1)	24.8 (3.9)	28.7 (0.9)	55
Gungor et al. (2005)	32	12 ^h 10 ⁱ	10	72.5 (6.8) ^h 71.8 (5.8) ⁱ	71.2 (5.2)	19.4 (3.2)	29.4 (0.5)	60

Hamberger et al. (1995)	26	6	10	67.1 (3.4)	67.0 (4.7)	--	--	62
Hirata et al. (2000)	38	26	12	72.2 (7.5)	69.0 (3.3)	18.6 (4.3)	29 (1.3)	63
Iragui et al. (1996)	36	12	12	70.0 (7.8)	72.0 (5.4)	22.3 (3.4)	29.5 (0.9)	68
Jacob & Duffy (2014)	49	14	17	73.6 (2.1)	77.0 (1.8)	27 (0.7)	28.6 (0.3)	69
Kazmerski & Friedman (1997)	32	8	8	68.8 (2.7)	69.3 (7.3)	--	--	71
Kazmerski et al. (1995)	32	8	8	67.9 (8.3)	68.4 (5.4)	--	--	72
Kazmerski et al. (1997)	48	16	16	68.7 (6.6)	69.1 (6.5)	--	--	73
Kowalewski & Murphy (2012)	20	--	10 ^d 10 ^e	--	69.6(5.0) ^d 69.0(3.5) ^e	--	--	74
Kraiuhin et al. (1990)	40	14	15	79.4 (61-90)	74.0 (61-92)	--	--	75
Kraiuhin et al. (1989)	30	15	15	79.4 (61-90)	--	--	--	76
Lockwood et al. (2018)	55	13	19	73.3 (1.6)	71.2 (1.4)	24.8 (0.9)	29.0 (0.2)	84
Marsh et al. (1990)	35	18	17	65.2 (5.8)	64.4 (6.7)	24.7 (1.3)	29.6 (0.7)	88
Mathalon et al. (2003)	32	12	10	76.2 (5.7)	75.3 (5.1)	20.7 (2.7)	29.6 (0.5)	89
Morgan & Murphy (2002)	24	12	12	72.8(7.3)	73.9(6.4)	--	--	92
Morgan & Murphy (2012)	20	--	10 ^d 10 ^e	--	70.2(2.9) ^d 71.2(3.6) ^e	--	--	93
Murphy et al. (2009)	20	--	10 ^d 10 ^e	--	75.1(8.3) ^d 71.0(6.1) ^e	--	27.0(2.7) ^d 26.1(2.8) ^e	95
O'Mahony et al. (1996)	30	18	12	74.5 (4.3)	72.7 (4.7)	--	--	96
O'Mahony et al. (1993)	57	16	15	78.0 (5.7)	77.5 (3.8)	23.4 (1.9)	28.9 (1.1)	97
Olichney et al. (2006)	22	11	11	79.4 (7.2)	77.1 (2.9)	22.9 (3.9)	29.6 (0.5)	99

Ostrosky-Solis et al. (1998)	30	10	10	75.4 (5.2)	67.8 (4.7)	16.5 (3.9)	27.2 (3.8)	103
Papadaniil et al. (2016)	63	21	21	70.0 (6.8)	67.0 (2.7)	22.6 (3.4)	28.9 (0.9)	105
Patterson et al. (1988)	50	15 [†]	15	60-86	57-81	18.3 (4.8)	28.1 (1.4)	110
Pedroso et al. (2018)	54	24	30	76.9 (5.3)	74.1 (5.6)	19.8 (4.5)	24.6 (4.0)	111
Phillips et al. (2004)	45	14	15	70.6 (7.0)	75.2 (5.5)	22.9 (3.7)	28.8 (1.2)	114
Polich et al. (1990)	32	16 [‡]	16	--	--	--	--	118
Revonsuo et al. (1998)	26	9	17	67.1 (8.3)	64.7 (4.0)	18 (6.7)	27.7 (1.8)	123
Rugg et al. (1994)	38	11	11	68.5 (7.1)	64.9 (5.1)	20.6 (3.3)	28 (1.5)	126
Schwartz et al. (1996)	36	12	12	67-81	63-86	--	--	129
Sumi et al. (2000)	108	34	39	70.0 (6.6)	68.5 (4.9)	--	--	135
Taler et al. (2009)	49	10	19	82.4 (5.4)	74.68 (7.6)	--	--	137
Tsolaki et al. (2017)	63	21	21	70.0 (6.8)	67.0 (2.7)	22.6 (3.4)	28.81 (0.9)	139
van Deursen et al. (2009)	55	15	20	75.2 (6.9)	69.5 (6.1)	20.8 (2.7)	29.3 (0.8)	142
Wang et al. (2013)	38	7	16	68.6 (2.9)	69.3 (1.8)	21.5 (0.8)	29.3 (0.5)	145
Wetter & Murphy (2001)	20	--	10 ^d 10 ^e	--	75.7(7.7) ^d 75.3(6.4) ^e	--	28.2(1.1) ^d 28.5(1.1) ^e	147
Wolk et al. (2005)	24	12	12	55-80	65-86	25.1 (3.2)	29.3	150
Yamaguchi et al. (2000)	50	16	18	68.5 (8.0)	69.6 (9.3)	--	--	152

Notes: AD = Alzheimer's disease; HC = older adults (controls); ^aε3/ε3; ^bε3/ε4; ^cε4/ε4; ^dε4+; ^eε4-; ^fAD family history-; ^gAD family history+; ^hmild AD; ⁱmoderate AD; -- = data not available/reported; ^sample size included in analyses; ~all participants consulted memory disorder clinic; †included 3 subjects w/multi-infarct dementia;‡AD group included subjects w/memory deficits with no known cause or probable AD.

Table 5.

Summarized ERP Findings and Trends in 100 Studies of MCI, AD, and Apolipoprotein-E (APOE) $\epsilon 4$ Included in the Review.

ERP Component & Metric	<u>Mild Cognitive Impairment</u>			<u>Alzheimer's Disease</u>			<u>Healthy/AD Risk (APOE $\epsilon 4$)</u>		
	N Studies	Majority Group Differences	Minority/ Notable Group Differences	N Studies	Majority Group Differences	Minority/ Notable Group Differences	N Studies	Majority Group Differences	Minority/ Notable Group Differences
N200									
Amplitude	18	None: 67% [11,22,28,51,53,78,81,83,86,94,120,142]	MCI<HC: 22% [12,29,30,145] (MCI^a<MCI^b, HC [12]); MCI>HC: 11% [106,107]	11	None: 82% [31,60,63,69,73,92,110,118,142]	AD<HC: 18% [84,145]	4	None: 100% [39,54,93,147]	---
Latency	19	None: 53% [28,29,51,78,81,83,86,106,120,142]	MCI>HC: 47% [11,12,22,30,53,90,94,107,145]; MCI^a>MCI^b, HC [90]	12	None: 42% [31,60,69,84,142]	AD>HC: 42% [92,96,110,118,135], trend 8% [145]; AD<HC: 8% [63]	4	$\epsilon 4+>\epsilon 4-$: 100% [39,54,93,147]	---
P300									
Amplitude	29	None: 55% [11,22,28,29,30,46,51,78,94,105,106,107,114,133,139,142]	MCI<HC: 38% [12,23,53,57,59,81,83,86,138,145,148]; MCI^a<MCI^b, HC [12]; MCI>HC: 7% [82,120]	25	AD<HC: 56% [3,4,13,43,60,63,71,84,89,114,118,142,145,152], trend 4% [42]	None: 40% [31,47,69,72,73,92,105,110,126,139]	4	None: 100% [39,54,93,147]	---

Latency	29	None: 59% [22,23,28,29, 30,46,57,59, 81,86,94,105, 107,114,120, 133,139]	MCI>HC: 41% [11,12,50,51, 53,78,83,106, 138,142,145, 148]; MCI^a>MCI^b,HC [12]	30	AD>HC: 60% [3,43,60,63, 71,76,88,92, 96,97,105, 110,111, 118,135, 139,142, 152], trend 7% [52,145]	None: 27% [4,31,47,69, 75,84,114, 126]; AD<HC: 7% [13,72]	5	ε4+>ε4-: 60% [93,95,147]	None: 40% [39,54]
N400									
Amplitude	6	MCI<HC: 50% [1,48,64]	None: 33% [100,154]; MCI>HC: 17% [137]	17	AD<HC: 65% [5,19,45, 55,62,68, 99,103,123, 129,150]	None: 24% [42,71,126, 137°]; AD>HC: 12% [43,137°]	1	---	ε4+>ε4- RH, ε4+<ε4- midline [73]
Latency	2	---	MCI>HC: 50% [100]; None: 50% [154]	9	AD>HC: 56% [19,42,43, 68,129], trend 11% [99]	None: 33% [71,103,126]	---	---	---
Late Positive Component (LPC)									
Amplitude	3	MCI<HC: 67% [16,100]	MCI>HC LH, MCI<HC RH [67]	6	AD<HC: 50% [45,99,123]; None: 50% [19,62,129]	---	---	---	---
Latency		---	None: 100% [100]	---	---	None: 100% [19]	---	---	---
Parietal Effect (PE)									
Amplitude	4	None: 50% [48,64]	MCI<HC: 25% [154], trend 25% [1]	---	---	---	---	---	---

Latency			---	---	---	---	---	---	---
Late Positive Potential (LPP)									
Amplitude	3	MCI<HC:	---	---	---	---	---	---	---
		100%							
		[16,116,146]							
Latency			---	---	---	---	---	---	---
Slow waves (SW)									
Amplitude	2	MCI>HC:	---	---	---	---	---	---	---
		100%							
		[30,131];							
		MCI^c>MCI^d,							
		HC [30]							
Latency	2	MCI>HC:	---	---	---	---	---	---	---
		100%							
		[106,107]							

Note: Only components analyzed in at least three studies are included; [text reference #]; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease; HC = older adults (controls); RH = right hemisphere; ¹includes early frontal effect; [°]included twice (results differed across comparisons); ^apMCI = progressing MCI; ^bnpMCI = non-progressing (stable) MCI; ^csdMC = single-domain (amnestic) MCI; ^dmdaMCI = multi-domain amnestic MCI; None = no significant group effects; -- = not investigated/reported.