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Keywords

Alzheimer's disease, apolipoprotein E ε4, compensation, event-related potentials, executive function, inhibition (psychological), neural recruitment

Abstract

Background:

Despite advances in understanding Alzheimer's disease (AD), prediction of AD prior to symptom onset remains severely limited, even when primary risk factors such as the apolipoprotein E (*APOE*) ε4 allele are known.

Objective:

Although executive dysfunction is highly prevalent and is a primary contributor to loss of independence in those with AD, few studies have examined neural differences underlying executive functioning as indicators of risk for AD prior to symptom onset, when intervention might be effective.

Methods:

This study examined event-related potential (ERP) differences during inhibitory control in 44 cognitively intact older adults (20 ε4+, 24 ε4-), relative to 41 young adults. All participants completed go/no-go and stop-signal tasks.

Results:

Overall, both older adult groups exhibited slower reaction times and longer ERP latencies compared to young adults. Older adults also had generally smaller N200 and P300 amplitudes, except at frontal electrodes and for N200 stop-signal amplitudes, which were larger in older adults. Considered with intact task accuracy, these findings suggest age-related neural compensation. Although ε4 did not distinguish elders during go or no-go tasks, this study uniquely showed that the more demanding stop-signal task was sensitive to ε4 differences, despite comparable task and neuropsychological performance with non-carriers. Specifically, ε4+ elders had slower frontal N200 latency and larger N200 amplitude, which was most robust at frontal sites, compared with ε4-.

Conclusion:

N200 during a stop-signal task is sensitive to AD risk, prior to any evidence of cognitive dysfunction, suggesting that stop-signal ERPs may be an important protocol addition to neuropsychological testing.

INTRODUCTION

Despite significant advances in the understanding of cognitive changes in advancing age and Alzheimer's disease (AD), the ability to accurately predict successful aging versus decline due to AD is poor. The pathophysiology of AD begins years, and possibly even decades, before the onset of clinical symptoms [1], which highlights the importance of identifying 'biomarkers' to target early indicators of AD while intervention might still be effective [2]. Biomarkers, or preclinical markers, are factors that can offer objective indices of structural or functional differences that can predict and track disease [3]. Much focus has been on the ε4 allele of the Apolipoprotein E (*APOE*) gene as the primary risk factor, secondary to age, for late-onset (sporadic) AD [4]. In older age, ε4 is associated with poorer memory,

greater rate of decline over time, and functional and structural neural differences even prior to cognitive dysfunction [5–12]. Yet, there is poor consensus about the role of *APOE* ε4 in cognition until late adulthood (e.g., [13, 14]), and moreover, on its own it is not a reliable predictor of conversion to AD—as few as 50% ever convert (e.g., [1, 15–17]). Genetic factors are constrained as biomarkers when disease conferral rate is not definitive. Indeed, as no single factor has been effective in predicting AD [18], additional predictors are needed that can complement ε4 in the pursuit of early detection [1, 19].

Although preclinical AD risk often focuses on me-mory and the temporal lobes, executive functioning (e.g., manipulating, switching, monitoring, and inhibiting [20]) declines earlier [21, 22] and may be more sensitive to AD than memory [1, 23, 24]. Despite being rarely assessed in preclinical risk studies, executive functions are more critical than memory for maintaining the activities of daily living (ADLs) necessary for independent, high-quality life [4, 25]. Complex attentional control tasks, such as the Stroop task, assess a type of higher-order executive functioning [26] that has been shown to tap later conversion to AD when memory does not, even when *APOE* ε4 inheritance is controlled [24, 27]. These findings suggest that memory deficits may even occur secondarily to deficits in complex attentional control [28–30], and indicate that such tasks, which provoke a strong response prepotency may be most likely to reveal early, subtle effects. Notably, poorer executive functioning has also been shown in *APOE* ε4 carriers, in both studies of humans [5, 14, 31–33] and in mice [34].

Subtle losses of executive functions in older adults reflect their foundations in frontal lobe functioning, which is particularly noted for showing early compensatory activation in older adults as an offset to declining function in other regions as they degrade and lose efficiency (e.g., [35–39]). Furthermore, complex attention and executive control tasks have evidenced compensatory neural activation particularly in prefrontal cortex associated with the degree of AD pathology using cerebrospinal fluid and specialized radioactive tracer scans [40].

Both longitudinal studies of AD conversion and techniques that can directly measure AD neuro-pathology are of critical importance. Yet, they are expensive, time consuming and/or invasive. Early predictors that allow identification of those most at risk for future cognitive decline is an urgent need that such studies cannot easily address. Additional markers that are more accessible and cost-effective are essential. Importantly, evidence of neural compensation has been demonstrated in cognitively intact APOE ε4 carriers, although this work is almost entirely with memory tasks (e.g., [9, 41–44]). Compensation in frontal networks during executive functioning tasks would be expected to occur earlier than task-related changes, and perhaps earlier than memory tasks. As such, tapping these frontal executive networks non-invasively would have distinct advantages toward developing an early index of AD risk.

Among the primary executive functions, the ability to inhibit habitual responses is particularly sensitive to aging and is impaired in AD [45–48]. Inhibitory control, as a complex attentional control process with high response prepotency, is considered foundational to functioning in other cognitive domains [29, 30]. It is particularly reliant on prefrontal functioning [49, 50] and is often assessed using go/no-go and stop-signal tasks in which participants respond to ‘go’ stimuli while inhibiting responses to ‘no-go’ stimuli or targets interrupted by a stop signal. Thus, examining preclinical risk for AD using inhibitory control might be particularly fruitful with measures that tap neural function, as these changes would be expected to occur earlier than task performance changes.

Event-related potentials (ERPs) [51] are an application of electroencephalography where voltage changes reflect neural activity locked in time to specific stimuli. They are particularly advantageous for capturing real-time neural processing of stimuli even when no behavioral response occurs, such as during inhibition. Such studies have focused predominantly on the N200 and P300 components. N200 is typically maximal over anterior electrodes [52] and associated with improbable or deviant events in a task [51, 53, 54], reflecting conflict monitoring and the act of determining whether to attempt to withhold a response [52, 55]. P300, typically maximal at central-posterior sites, is associated with attentional processing and resource allocation particularly in the context of inhibitory demands [56–59]. Thus, it reflects the more general task of performance evaluation and error detection [60]. Most aging studies of N200 and P300, however, use "oddball" detection paradigms, reflecting simple target attention and detection [61, 62], rather than executive or inhibitory tasks. Target response and component latencies in oddball paradigms are typically slower in older adults [55], with decreased N200 (conflict monitoring; Fz) and P300 (attention, Cz, Pz) amplitudes [63, 64].

Although rare in aging, executive tasks used with ERPs have provided more nuanced findings than oddball tasks. For example, in a go/no-go task with carefully controlled task difficulty, older adults had slower response time and delayed 'go' latency in posterior electrodes (P300 at Pz), but larger 'no-go' amplitude at central-anterior electrodes [P300 at Cz; 65]. A similar go/no-go task produced prolonged latency of N200 and P300 'no-go' ERPs in elders, accompanied by reduced posterior amplitudes and increased frontal amplitudes [66]. These latter findings are notably consistent with what is typically reported using fMRI with go/no-go (e.g., [45, 67]), supporting both the processing speed hypothesis of aging [68] and compensatory theories of aging that show increased activation, often with a frontal shift and reduced neural activity in other task relevant areas [35–39, 45, 67].

In AD and mild cognitive impairment (MCI), N200 and P300 have primarily been examined with simple oddball paradigms, frequently along midline electrodes. Studies typically show reduced amplitude and prolonged latency [19, 69, 70], consistent with neurogenerative disorder-related atrophy and activation reduction [71, 72]. Few executive tasks have been examined in MCI, but existing studies suggest reduced N200 [73, 74] or P300 amplitude [75, 76] and prolonged N200 latency [74, 77–79] in MCI. One AD study using an Eriksen Flanker task similarly reported reduced N200 and P300 amplitudes and a trend toward prolonged latency [80].

Despite the sensitivity ERPs might have as markers of emerging AD-related neural dysfunction, they have only rarely been studied in this context. Indeed, regarding *APOE* ε4 carriers, N200 and P300 have almost exclusively been examined after diagnosis with MCI or AD, rather than in cognitively intact elders. *APOE* ε4 appears to exacerbate the latency effects shown in MCI and AD studies that used oddball paradigms [81–83], although amplitude effects have been rare; P300 was reduced in ε4 carriers in only one study [84]. The only study employing a more complex task, visual-spatial working memory, however, found both intact and MCI-diagnosed ε4 carriers had smaller posterior P300 amplitude, along with greater right parahippocampal amplitude [85]. This latter finding compares with aging ERP studies using go/no-go tasks [66], as well as fMRI studies with intact *APOE* ε4 carriers using memory tasks (e.g., [9, 41–44]) and covert attention tasks [86]. Each of these is also consistent with compensatory theories of aging, exacerbated by *APOE* ε4 [37].

Importantly, inhibitory control has not been studied with ERPs in cognitively intact *APOE* ε4 carriers; very few studies exist at all using cognitive rather than sensory tasks in these elders (see [70]). This is remarkable given the sensitivity of ERPs to aging and the possibility that they could detect disease earlier than behavioral or neuropsychological testing alone. To address this gap in the literature, we examined midline N200 and P300 ERPs elicited during inhibitory control (go/no-go and stop-signal tasks) in healthy, cognitively intact older adult *APOE* ε4 allele carriers and comparable non-carriers. To contextualize these older groups and distinguish the effects of age from the effects of *APOE* ε4, we compared them with a reference group of non-genotyped young adults. Given the paucity of studies in this area, we evaluated *APOE* ε4 effects in the context of prominent aging theories that postulate compensation and a frontal shift in brain activation by examining N200 and P300 along the midline from frontal (Fz) to parietal (Pz) sites. We hypothesized slower response times and prolonged latencies in older adults relative to younger adults, as these are found in a number of ERP paradigms. Amplitude was more difficult to predict but we anticipated smaller posterior and larger anterior amplitude in older relative to younger adults [66]. Based on limited work with oddball paradigms and one study using a complex (albeit non-inhibitory) task [85] and compensatory aging theory [35, 37, 38], we tentatively predicted that inhibition-related ERPs in ε4 carriers would exhibit delayed latency, smaller posterior amplitude, and larger anterior amplitude relative to non-carriers.

MATERIALS AND METHODS

Participants

Young adults ($n = 42$) were undergraduate students who participated for course credit; they were not genotyped and served as a reference group. Older adult participants ($n = 49$, minimum 12 years of education) were recruited from the local community via newspaper advertisements emphasizing participation of healthy participants with a family member diagnosed with AD in order to increase the likelihood of obtaining a balanced sample of *APOE* ε4 allele carriers [87]. Older adults were compensated for their time. One older adult (*APOE* ε4 carrier) was excluded from analysis due to evidence of impaired cognition during dementia screening, reducing the older sample to 48, including 23 *APOE* ε4-positive (*APOE* ε4+, 22 ε3/ε4, 1 ε4/ε4) and 25 *APOE* ε4-negative (*APOE* ε4-; 22 ε3/ε3; 3 ε2/ε3) participants. Genetic results were determined using a blood sample subjected to a real-time PCR-based single nucleotide polymorphism analysis; results were not divulged to participants. The local Institutional Review Board reviewed and approved all procedures.

Measures

Inhibitory control tasks

We employed tasks that are routinely used in behavioral and clinical studies to measure inhibitory control. These included a modified go/no-go task similar to what we have used in past (Go, No-go) [88] and a modified stop-signal task (Stop) [89]. For each task, a serial stream of black letters was presented against a light grey background on a computer screen at a rate of 750 ms per letter with a 0 ms interstimulus interval. The Go task required responding as quickly as possible to specified targets ("r" and "s") with a key press (504 stimuli, 78 targets). It serves to establish a prepotent response and evaluates attention and psychomotor speed. The Stop task resembled the Go task, except that a response was to be withheld if a stop-signal occurred, represented by a red box flashed for 100 ms on the screen after the target; the stop signal delay (SSD) varied at 125 ms or 200 ms to prevent

predictability while also allowing for high accuracy, maintaining group comparability and a high percentage of ERP trials for analysis [89, 90]. This version included 684 letter stimuli, 81 targets and 36 stop trials. The No-go task also resembled the Go task except that participants responded to one target while withholding response to the other, in alternation. This version included 828 letter stimuli, 99 targets and 36 no-go trials. Go/no-go tasks tap inhibition through selective execution of a response (i.e., intrinsic), while stop-signal tasks tap inhibition through selective retraction of a response (i.e., extrinsic) [91, 92]. Practice blocks of trials were used to acclimate participants to the task demands. Test blocks incorporated rest intervals to remind participants of the instructions and to reduce fatigue. Outcome measures included accuracy (Percent Correct Target Trials (PCTT; Go), Percent Correct Inhibitory Trials (PCIT; Stop and No-go)) and response latency (Reaction Time to Targets (RTT; Go) and Stop-signal Reaction Time (SSRT; Stop); no estimate of response time is possible for No-go). SSRT denotes the latency in the stop process as estimated from distribution of observed RTTs in the Stop task, combined with the inhibition function [90].

Standardized testing

Participants each completed several traditional, standardized tests. First, the Mattis Dementia Rating Scale - Second Edition (DRS-2) [93, 94] is a cognitive screening measure assessing attention, conceptualization, initiation/perseveration, construction, and memory. A DRS-2 total score cut-off of 130 was used as a marker of intact cognitive ability for inclusion in the study for older adults [95]. The North American Adult Reading Test (NAART) was administered to all participants as a measure of verbal ability and crystalized intelligence [96]. Other standardized neuropsychological tests focused on executive functioning and processing speed, as relevant to the experimental task in this study. These commonly used and validated tests included the Trail-making Tests (part A and B) [97], the Symbol-Digit Modalities Test (SDMT) [98], digit copy (processing speed) [99], the Controlled Oral Word Association Test (phonemic fluency) [100], and semantic fluency (animals).

EEG data acquisition and event-related potentials

Continuous EEG data were collected using a 64-channel active electrode actiCAP (Brain Products) with international 10–20 system arrangement (FCz reference, AFz ground) and recorded in DC mode with a low-pass hardware filter at 100 Hz and a 500 Hz sampling rate using Neuroscan SynAmps2, with impedances kept under 50 kΩ, and Neuroscan software (Scan 4.5). EEG data were processed off-line using EEGLAB [101] via MATLAB (version 7.12, The MathWorks) for extraction of ERPs. Raw continuous data were imported, and channels were rejected as needed upon visual inspection to eliminate channel-level artifacts. Number of removed channels did not significantly differ between groups ($ps > 0.32$; both age groups: range = 0–4, median = 0). EEG data were re-referenced to a common average of all electrodes. Low frequency and power line noise were removed using a band-pass filter from 0.2 to 100 Hz and notch-filter from 59 to 61 Hz. An independent component analysis (ICA) (AMICA) [102] was used to decompose the continuous data into independent components. Components reflecting eye blinks were rejected and removed from the data based on visual inspection.

Data were then segmented around stimulus-locked triggers for each of the stimulus conditions with a 100 ms pre-stimulus (i.e., target letter onset) to 1500 ms post-stimulus window, with a 100 ms baseline correction; Stop trial epochs referenced the stop-signal onset. Epochs were rejected as appropriate

based on visual inspection. Only trials with correct responses were included. Epochs were then averaged separately for each of the task conditions (Go, No-go, Stop). A final low-pass filter of 20 Hz (zero-phase, 4th-order, Butterworth) was used to eliminate non-brain-related activity. For each condition, peak amplitude and peak latency were computed at Fz, FCz, Cz, and Pz between the range of 100 and 300 ms for N200 and 300 and 700 ms for P300.

Procedure

Participants completed two testing sessions, app-roximately 1 week apart. They were tested individually on both occasions and completed informed consent at the beginning of each session. The first session included administration of standardized testing. At the second session, EEG data were collected during the inhibitory tasks.

Participants were situated in front of a computer and instructed to limit gross motor movements as much as possible to reduce noise in the EEG signal. The inhibitory tasks were presented in MATLAB (version 7.12, The MathWorks); standard task order was used (Go, Stop, No-go). Instructions were read aloud and also appeared on the screen; questions regarding task instructions were answered as needed. Corrective feedback was provided throughout the practice blocks of each task. No feedback was provided during the test blocks of the task.

Data analyses and exclusions

Significance was set at $p < 0.05$. One-way analysis of variance (ANOVA with Tukey LSD), or Chi-square for frequency data, was used to compare groups on demographic measures. To limit the influence of Type I error, task performance and testing variables were each examined with multi-variate ANOVA (MANOVA), with follow-up univariate ANOVA and Tukey LSD contrasts for significant effects involving Group. ERP data were examined with an omnibus mixed ANOVA (3 (Groups: young, older ε4+, older ε4-) x 3 (Tasks: go, stop-signal, no-go) x 4 (Electrodes; Fz, FCz, Cz, Pz)) for amplitude and latency of the N200 and P300 components (i.e., four models; with Greenhouse-Geiser correction for sphericity). Results of interest were the main effects of Group and the 3-way interactions (see Table 2); all interactions with Group were significant. Due to this omnibus approach, five subjects were removed from all analyses for the following reasons: two ε4+ elders failed to demonstrate understanding of (only) the stop-signal task, and one subject from each of the three groups had poor quality ERP data on one or more of the tasks (e.g., motion artifact). Thus, the final sample shown in analyses, tables, and figures includes 20 ε4+, 24 ε4-, and 41 young adults. Analysis of the testing variables, however, had 40 young subjects due to one missing Digit Copy score.

Table 2 Summary of significant effects of *post-hoc* contrasts (LSD) from significant 3-way (Group by Task by Electrode) interactions for N200 and P300 amplitude and latency (see Results), showing group contrast effects, and electrode contrast effects

Task		Group contrast effects					Electrode site contrast effects			
		N200		P300			N200		P300	
	Site	Amplitude	Latency	Amplitude	Latency	Group	Amplitude	Latency	Amplitude	Latency
Go	Fz	-	Y > ε4+ =ε4-^	ε4+ =ε4- > Y^	Y < ε4+ =ε4-~	ε4+	-	F, FC < C~	P > C^	P > all^
	FCz	-	Y > ε4+ =ε4-^	ε4+ =ε4- = Y~	-	ε4-	F, FC > C~	P>all~	FC > C~	P > all^
	Cz	Y > ε4+ =ε4-^	Y > ε4-~	Y > ε4+ =ε4-~	Y > ε4-=ε4-^	Young	F < all*	FC, C > P^	P > all*	F < all*
	Pz	Y > ε4+ =ε4-^	-	Y > ε4+ =ε4-*	Y < ε4+ =ε4-^					
Stop	Fz	ε4+ > Y > ε4-^	ε4+ > ε4-=Y^	-	-	ε4+	FC, C > F, P*	P < all*	P > C~	P < all^
	FCz	ε4+ > ε4-=Y*	ε4+ =ε4- > Y*	Y > ε4+^	Y < ε4+ =ε4-*	ε4-	F < all^	F, *P* < FC, C^	-	P < FC, C^
	Cz	ε4+ > ε4- > Y*	ε4+ =ε4- > Y*	Y > ε4+ =ε4-*	Y < ε4+ =ε4-*	Young	F, FC > P~	P < C < FC < F^	F < all*	F > all~
	Pz	ε4+ =ε4- > Y*	ε4+ =ε4- > Y*	Y > ε4+ =ε4-*	Y < ε4-*					
No-go	Fz	-	-	ε4+ =ε4- > Y^	Y < ε4+ =ε4-~	ε4+	-	-	F, FC > C^	P > C^
	FCz	-	-	-	-	ε4-	F > FC~	F, FC < P~	-	P > C^
	Cz	Y > ε4+ =ε4-~	-	Y > ε4+^	Y > ε4+ =ε4-^	Young	F, FC < C, P^	-	P > all*	F < all*
	Pz	Y > ε4+ =ε4-~	ε4+ > Y~	Y > ε4+ =ε4-*	Y < ε4+~					

ε4, Apolipoprotein E ε4; ε4-, non-carrier older adult; ε4+, carrier older adult; Y, young adult. Electrode sites (midline, z), *F* = frontal, FC = frontal-central, *C* = central, *P* = parietal. *$p < 0.001$, ^$p < 0.01$, ~$p < 0.05$.

RESULTS

Sample demographics and descriptive data are presented in Table 1. The groups did not significantly differ by sex distribution and the older adult genetic risk groups did not significantly differ on the DRS-2 or on the executive functioning and processing speed measures (see Table 1). The typical age difference (older adults slower and less accurate than young adults on neuropsychological testing) was, however, significant in all comparisons except for the COWAT (see Table 1). The *APOE* ε4+ group had greater educational attainment than either the *APOE* ε4- group or the young group, which is considered protective and would be expected to attenuate rather than accentuate any group differences [103]. As education also did not contribute to models when tested as a covariate, it was not included in the final analyses.

Table 1 Sample demographics, task performance, and neuropsychological testing by group (mean (±SD)) with omnibus MANOVA (task, testing) and *post-hoc*/univariate effects

	Older adults ($n = 44$)		Young adults ($n = 41$)	*Stat*[a], *p*, η_p^2	Effect
	APOE ε4+($n = 20$)	*APOE* ε4- ($n = 24$)			
Demographics/screening					
Age (y)	78.4 (4.4)	79.7 (4.9)	19.9 (2.7)	> 2000, < 0.001, 0.99	(ε4+ = ε4-) > Y
Education (y)	16.0 (3.1)	13.9 (1.8)	14.5 (2.3)	6.7, < 0.01, 0.13	ε4+ > (ε4- = Y)
Sex (% female)	80.00%	66.70%	73.20%	0.99, > 0.61, 0.11	–
DRS-2	138.0 (3.4)	138.9 (3.0)	-	0.97, > 0.34, 0.02	–
Tasks ($F(10,158) = 7.72$, $p < 0.001$, 0.33)					
Go PCTT	99.5 (1.0)	99.5 (0.7)	99.5 (1.5)	< 0.1, > 0.99, 0.00	–
Stop PCIT	73.5 (14.9)	75.8 (9.4)	77.9 (12.6)	0.9, > 0.43, 0.02	–
No-go PCIT	77.1 (15.3)	78.1 (15.3)	82.5 (13.9)	1.2, > 0.31, 0.03	–
Go RTT (ms)	689.2 (49.0)	670.9 (46.8)	596.5 (39.3)	38.6, < 0.001, 0.49	(ε4+ = ε4-) > Y
Stop SSRT (ms)	544.4 (35.1)	541.5 (39.3)	452.0 (45.1)	51.2, < 0.001, 0.56	(ε4+ = ε4-) > Y
Testing[b] ($F(14,152) = 6.14$, $p < 0.001$, 0.36)					
NAART	41.1 (7.6)	38.9 (8.7)	31.5 (11.0)	8.2, > 0.01, 0.17	Y< (ε4+ = ε4-)
TMT-A (sec)	32.7 (10.5)	33.5 (8.9)	20.4 (5.0)	27.8, < 0.001, 0.41	(ε4+ = ε4-) > Y
TMT-B (sec)	77.0 (27.5)	85.5 (26.9)	57.1 (20.5)	11.0, < 0.001, 0.21	(ε4+ = ε4-) > Y
Copy (sec)	74.4 (12.4)	75.6 (10.9)	59.6 (9.9)	21.7, < 0.001, 0.35	(ε4+ = ε4-) > Y
SDMT	40.9 (8.9)	42.8 (8.8)	63.6 (9.5)	60.6, < 0.001, 0.60	(ε4+ = ε4-) < Y
COWAT	43.2 (11.1)	41.1 (11.2)	36.9 (10.8)	3.0, > 0.06, 0.07	–
Category	18.3 (4.8)	18.3 (4.6)	23.4 (4.9)	11.3, < 0.001, 0.22	(ε4+ = ε4-) < Y

APOE, Apolipoprotein E; DRS-2, Dementia Rating Scale-Second Edition total score; RT, response time; PCTT, Percent Correct Target Trials; PCIT, Percent Correct Inhibitory Trials; RTT, Reaction Time to Targets; SSRT, Stop-signal Reaction Time; NAART, North American Adult Reading Test; TMT, Trail-making Tests; Copy, Digit Copy; SDMT, Symbol-digit Modalities Test; COWAT, Controlled Oral Word Association Test (phonetic fluency); Category, semantic fluency. [a]Univariate/*post-hoc* tests, *F* with *p* and partial-eta^2, except Sex (χ^2, with *Phi*) and DRS-2 (*t*, with partial-eta^2); effect indicates results of *post-hoc* Tukey LSD between groups; [b]young sample = 40 for this omnibus/*post-hoc* tests set; 1 subject missing Digit Copy.

Task behavioral data analyses

Behavioral task descriptive statistics are presented by group in Table 1. The groups did not significantly differ on any task accuracy metric (*p*s 0.09 to 0.99). However, as expected, young subjects were significantly faster (*p*s < 0.001) than either older group (which did not differ, *p*s > 0.4) in responding to targets (Go, $F(2,86) = 36.6$, $p < 0.001$, $\eta_p^2 = 0.46$) and estimated stop-signal reaction time (SSRT, $F(2,85) = 53.0$, $p < 0.001$, $\eta_p^2 = 0.56$). Thus, the behavioral task data compared closely with standardized testing, showing age differences in speed, but intact task performance in older adults, whose performances were not distinguishable by gene status.

ERP analyses

Omnibus mixed ANOVAs (3 Groups X 3 Tasks X 4 Electrodes) are presented for the N200 and P300 components, separately for amplitude and latency, with follow up contrasts for significant effects involving Group. Figure 1 displays the grand average ERP waveforms for accurate stop-signal trials for all three groups, highlighting the N200 and P300 peaks, at each of the four electrodes studied. Figure 2 (amplitude) and Fig. 3 (latency) show each group at each electrode, for each component and task (mean (±SEM)).

Fig. 1 Grand average wave-forms for correct stop-signal trials by each group (Young, Older *APOE* ε4+, Older *APOE* ε4-) at midline electrodes (Fz, FCz, Cz, and Pz), across the pre- to post-stimulus recording epoch (y axis = microvolts; x axis = milliseconds). The analysis windows for N200 and P300 are highlighted.

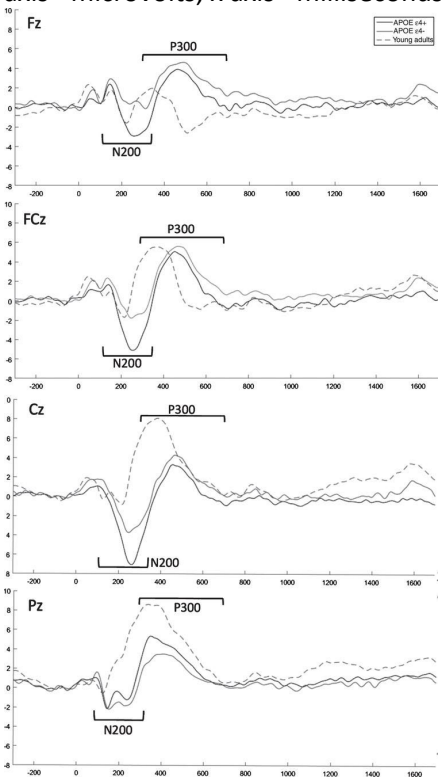


Fig. 2 Average ERP amplitude ± SEM; (y axis = microvolts) at each midline electrode is shown by subject group (Young, Older *APOE* ε4+, Older *APOE* ε4-) separately for N200 and P300 and for each task, Go, Stop-signal, and No-go. Corresponding significant group differences are specified in Table 2.

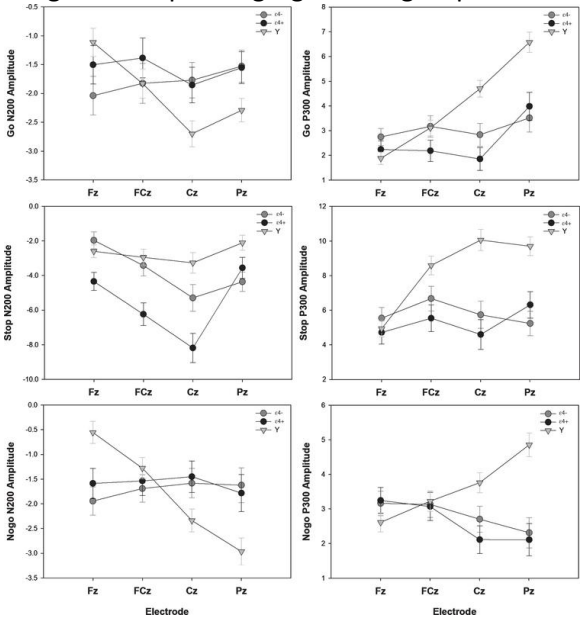
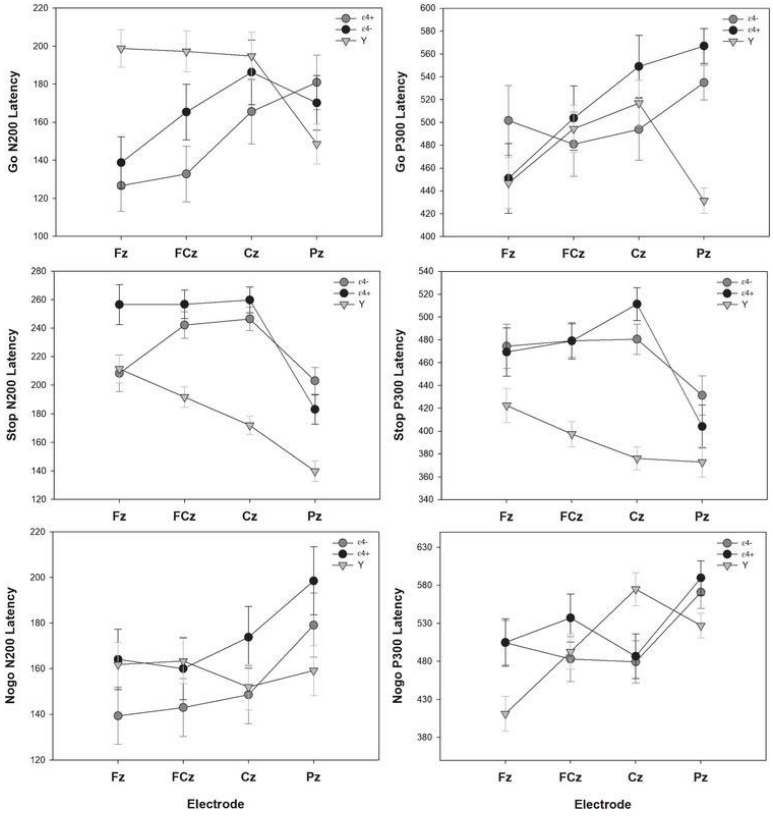


Fig. 3 Average ERP latency ± SEM; (y axis = milliseconds) at each midline electrode is shown by subject group (Young, Older *APOE* ε4+, Older *APOE* ε4-) separately for N200 and P300 and for each task, Go, Stop-signal, and No-go. Corresponding significant group differences are specified in Table 2.



N200 amplitude

There was a non-significant trend of Group ($F(2,82) = 3.0$, $p < 0.06$, $\eta_p^2 = 0.07$), due to generally greater amplitude (i.e., more negative) in ε4+ elders relative to young adults ($p < 0.02$). The Group X Task

interaction ($F(2.5,104.0) = 14.3$, $p < 0.001$, $\eta_p^2 = 0.26$) and Group X Electrode interaction ($F(3.6,148.1) = 2.8$, $p < 0.03$, $\eta_p^2 = 0.06$) were significant, as was the 3-way interaction of Group X Task X Electrode ($F(5.5,226.0) = 13.2$, $p < 0.001$, $\eta_p^2 = 0.24$). The 3-way interaction showed differences were primarily due to the Stop task. The results of follow-up contrasts are shown in Table 2. During Go and No-go, young adults had greater amplitude than either older group at Cz and Pz, but not at anterior sites. However, during successful Stops, ε4+ had greater amplitude than both ε4- and young at all sites except Pz, where they exceeded young but did not significantly differ from ε4- (see Fig. 2). ε4- exceeded young only at Cz and Pz. Electrode contrasts further demonstrated that young had maximal central-posterior amplitude for Go and No-go, but a more anterior shift for Stop. ε4- elders were more maximal at frontal-central sites for Go and No-go, but more posterior (and greater than young) during Stop. ε4+ elders had relatively equal activity across sites for Go and No-go, but fronto-central maxima specifically during Stop, which was greater than both other groups (see Table 2, Fig. 2). Thus, N200 amplitude (maximal at Cz, particularly during the Stop task) demonstrated a typical age effect during Go and No-go, with reduced amplitude in old relative to young particularly at central and posterior sites, but the Stop task highlighted the influence of both age and ε4. While all groups evidenced a more anterior distribution of activity during Stop than Go or No-go, ε4+ elders had greater amplitude than other groups across sites and ε4- elders had greater amplitude than young in central-posterior sites (see Fig. 2).

N200 latency

The main effect of Group was not significant ($F(2,82) = 2.5$, $p = 0.09$, $\eta_p^2 = 0.06$). The Group X Task interaction ($F(3.8,154.8) = 14.0$, $p < 0.001$, $\eta_p^2 = 0.26$) and Group X Electrode interaction ($F(4.5,184.3) = 5.5$, $p < 0.001$, $\eta_p^2 = 0.12$) were significant and clarified by a 3-way interaction of Group X Task X Electrode ($F(8.2,336.2) = 2.4$, $p = 0.01$, $\eta_p^2 = 0.06$) The young had longer latencies than both older groups at fronto-central sites during Go, shorter latencies than both older groups at all sites during Stop, and shorter latencies than ε4+ during No-go at Pz (see Table 2). ε4+ also had longer latency at Fz than ε4- for Stop; otherwise the two older groups did not differ. Electrode contrasts showed the young had longer anterior than posterior latencies during Go, while the older groups had the opposite pattern (see Table 2, Fig. 3). All groups had longer anterior N200 latencies for Stop than Go, but there was a larger shift to longer latency during Stop relative to Go in older adults, particularly at frontal-central sites. ε4+ elders had particularly prolonged Stop N200 latency at the frontal site (see Fig. 3).

P300 amplitude

There was a significant effect of Group ($F(2,82) = 9.3$, $p < 0.001$, $\eta_p^2 = 0.19$), with young adults exhibiting overall greater amplitude than both older groups (ps < 0.01). The Group X Task interaction ($F(2.6,107.1) = 4.8$, $p = 0.001$, $\eta_p^2 = 0.11$) and Group X Electrode interaction ($F(3.5,145.1) = 18.6$, $p < 0.001$, $\eta_p^2 = 0.31$) were significant. The 3-way interaction of Group X Task X Electrode ($F(6.7,273.7) = 3.9$, $p = 0.001$, $\eta_p^2 = 0.09$) clarified that the young had greater P300 amplitude for Cz and Pz than both older groups during Go, No-go (ε4+ only for Cz), and Stop (also FCz with ε4+; see Table 2). In contrast, at Fz, the older groups had larger P300 amplitude than the young during Go (also FCz) and No-go. The older adult groups did not significantly differ from each other. Electrode contrasts primarily highlighted the central-posterior maxima in young subjects and relatively smaller amplitude at Fz; the pattern in older adults was much less differentiated across sites

(see Table 2, Fig. 2). Taken together, older adults had reduced P300 amplitude in all three task conditions relative to young adults, but greater frontal amplitude, consistent with recruitment in older adults during Go and No-go. There were no specific effects of ε4+.

P300 latency

The main effect of Group was significant ($F(2,82) = 7.2$, $p = 0.001$, $\eta_p^2 = 0.15$), showing overall shorter P300 latency in young subjects compared with both older groups ($ps < 0.02$), who did not differ. The Group X Task interaction ($F(3.9,158.2) = 2.5$, $p < 0.05$, $\eta_p^2 = 0.06$) and Group X Electrode interaction ($F(4.7,192.0) = 5.3$, $p < 0.001$, $\eta_p^2 = 0.11$) were significant. The 3-way interaction of Group X Task X Electrode ($F(9.2,378.5) = 5.4$, $p < 0.001$, $\eta_p^2 = 0.12$) clarified that the young had shorter P300 latency at Fz during all three tasks than either older group, as well as during Go at Pz and Stop at Cz (see Table 2). They also had shorter latency at Pz during Stop relative to ε4- and during No-go relative to ε4+. The gene groups did not differ. Electrode contrasts showed that the older groups had longer latencies at Pz on each task relative to other sites, while young adults had shorter Fz latencies relative to all other sites on each task (see Table 2, Fig. 3). Thus, overall, older adults had longer P300 latency, particularly at the frontal and parietal electrodes (and at all electrodes for Stop), relative to young adults. There were no specific effects of ε4+ (see Fig. 3).

DISCUSSION

This study examined *APOE* ε4 genetic influences on inhibitory control in cognitively intact older adults, relative to a young adult reference group. The study focused on peak amplitude and latency for two ERPs that are commonly examined in the context of executive functioning, N200 (i.e., inhibitory control, conflict monitoring) and P300 (i.e., attention, resource allocation). Only a handful of prior studies have examined ERP amplitude or latency differences in cognitively intact *APOE* ε4 carriers; none have done so during inhibitory control. Overall, our findings reinforce age-related slowing of response times and ERP latencies, and reduced N200 and P300 amplitude in older relative to young adults. Older adult ε4-carriers and non-carriers primarily did not differ, either on task, psychometrics or ERPs. However, one effect fit our prediction: during the stop-signal task, *APOE* ε4 carriers had greater N200 amplitude from frontal through central sites, and longer frontal N200 latency than non-carriers (and young adults), indicative of greater dysfunction and exacerbated anterior shift in ε4 carriers in N200 during executive functioning.

Task and testing performance

Task response accuracy was comparable among groups for target trials (i.e., Go) as well as for inhibitory trials (i.e., Stop and No-go), but both older groups exhibited slower responses than young adults, as predicted. Accuracy and response time did not differ by *APOE* ε4. These findings are consistent with age-related slowing that is often found in speeded tasks [68, 104, 105]. This was further supported with standardized neuropsychological testing, in which the two older adult groups were comparable. Although some prior studies have found *APOE* ε4 or AD family history risk differences in behavioral tasks of executive functioning [5, 14, 23, 31, 32], our sample was older than typical (minimum age in both groups was 72), highly educated (12 to 20 years), and neuropsychological performance was well within expectations for age and education norms in both elder groups. Thus,

there was genuine group equivalence, thereby reducing the likelihood of finding group differences even at the neural level, but making them particularly important and revealing, where they existed.

Age differences in ERPs

As expected, the older adult groups in the present study tended to exhibit longer N200 and P300 ERP latencies than young adults. For N200, all groups had longer anterior latency for Stop relative to Go, but older adults exhibited a larger latency shift for Stop, particularly at frontal-central sites. Prolonged P300 latency was apparent in older adults particularly at both frontal and posterior sites, and at all but Fz during Stop, though with shorter P300 Cz latencies (Go, No-go) than young. These patterns are generally consistent with age-related cognitive slowing [68, 105] and relatively well-established trends of slowed N200 and P300 latencies with age, although some studies showed shorter Go latency for N200 in older adults [106, 107].

N200 and P300 amplitude differences emerged between young and old for all three task conditions. For both components, older adults had smaller amplitudes relative to young adults at central and posterior sites during Go and No-go, as well as for P300 during Stop. These findings are consistent with our hypothesis and the literature across a variety of tasks [63–66, 106].

Importantly, contrasting with other amplitude ef-fects, P300 amplitude was greater in the older groups than young at Fz during both Go and No-go. Furthermore, N200 during Stop produced significantly greater amplitude in older adults than in young adults, with the largest effects at frontal-central sites. Although even young subjects had larger frontal amplitude during Stop than Go, the differential was larger in older adults. Prior aging research on N200 amplitude has been inconclusive, but some studies, including some using less cognitively demanding oddball tasks [66], are consistent with this anterior shift finding [108, 109]. Thus, our robust findings suggest that assessing N200 during a stop-signal task captures the alerting and inhibitory demands that N200 indexes [106, 110, 111], thereby also better indexing age-related differences than oddball tasks. It is further notable that both the N200 and P300 patterns are consistent with some fMRI studies suggesting greater amplitude in elders at the most frontal sites examined, often with reduced activation at more posterior task-relevant sites [35, 37, 38, 45, 67]. Such findings are compatible with predictions made by compensatory models of cognitive aging (STAC) [37, 112] and those suggesting a posterior to anterior shift with age (PASA) [39]. Moreover, these findings reinforce the value of including executive functioning assessment in preclinical dementia prediction studies, as deficits are known to occur early in the disease course [1] and they are predictive of the ability to live independently [25].

APOE ε4 differences in ERPs

The cognitively intact groups of older adult *APOE* ε4 allele carriers and non-carriers were comparable on task performance, all psychometrics, and demographic factors. Similarly, no ε4 differences emerged for N200 or P300 components for the Go or No-go tasks. Yet, the Stop task did reveal important differences. Based on oddball tasks and one complex attention study [85], we tentatively predicted that ε4+ would exhibit delayed latencies relative to non-carriers. This effect was evident only at the frontal electrode for N200 during Stop. We also tentatively predicted smaller posterior amplitude but larger anterior amplitude in ε4+ versus ε4-. This was not supported in the Go or No-go tasks; instead,

both groups exhibited an age-related compensatory pattern of reduced central-posterior amplitude and greater frontal amplitude relative to young [37, 39, 112].

In contrast to No-go, in the Stop task, our ε4 hypothesis was supported for N200. More specifically, all groups had more anterior activity in Stop than Go or No-go, indicative of the demand it places on cognitive control. However, elders had greater amplitude than young at central-posterior sites, and ε4+ specifically exhibited greater N200 amplitude than young at all sites and greater than ε4- at all but Pz. This pattern was graded such that it was most robust at anterior electrodes. This is particularly notable given it occurred in the absence of any differences in task or neuropsychological performance between carrier groups. Therefore, the anterior shift effect was more nuanced than the tentative prediction, but in a task-consistent manner. That is, stop-signal tasks require effortful retraction of a selective motor response to an external, unpredictable cue, which requires more cognitive control than no-go tasks [89, 92, 113]. Thus, the differential ε4 effect at the neural level in N200 of Stop only (amplitude and latency) fits well with the greater demand Stop imposes on cognitive control than Go or No-go, and the alerting and inhibitory demands that N200 indexes [106, 110, 111]. This stop-signal finding is furthermore fitting with longitudinal studies that suggest complex attentional control can be more predictive of conversion to AD, even years later, than is afforded by memory measures [24, 27]. Finally, it strongly suggests that N200 during stop-signal tasks is sensitive to early neural decline associated with ε4+, even in very high-functioning elders. While several ERPs have been proposed as potential 'biomarkers of AD', most have focused on early sensory ERPs such as P50 [114]. The current findings suggest that later ERP components, which better reflect controlled processing during complex attention and executive tasks, may be more sensitive to early risk for dementia [19, 64, 70].

Importantly, additional research is needed to validate whether stop-signal N200 ERP distinctions between ε4+ and ε4- can be used to effectively predict the onset of AD. An important test of this idea could come from using the Stop-related N200 ERP to distinguish from amongst carriers of ε4, comparing it with detailed neuropsychological, biometric, and biological indices. In conjunction with long-term outcome studies of eventual converters, an 'index' might be developed, with defined cutoffs, that identifies early compensatory activity in those at particularly heightened risk of future cognitive decline. Given that only a subset of ε4 carriers develop AD, and that a proportion of non-carriers also develop AD, these studies would also be crucial toward determining whether ε4 is an essential element of this predictive index, or whether it can be applied regardless of their ε4 inheritance. Either way, if attainable, such an index would be an important complement to clinical assessment.

The analysis approach herein focused on a midline topographic analysis. This is a simple approach, but it has also been the predominant approach evident in N200 and P300 studies, particularly in MCI and AD samples. It was also valuable for examining frontal compensatory activity relative to aging and ε4 carriers. However, this approach was not meant to construe neural network activity in response to these tasks as single processes, in either amplitude or latency, that occurs across the scalp. Future analyses examining specialized regions of interest in these data would be of particular value toward discerning age- and gene-relevant differences in specific aspects of these tasks, their putative sources, and their temporal signatures.

The current study did not genotype young adults. Based on population statistics, 12–15% of these subjects might be ε4 carriers [115]. Evidence on the effects of *APOE* ε4 inheritance in young adults is conflicting, with findings of greater [42, 116, 117], lesser [118, 119], and equivalent activation between carriers and non-carriers [see 120], suggesting that detrimental effects of ε4 are only consistently established in older age. The goal of the present study was not on the lifespan influence of ε4. We sought instead to distinguish the contribution of ε4 from the more general effects of age on ERP responses during executive functioning in cognitively intact older adults. Thus, the young group served as a reference for age effects. While it leaves unclear what role ε4 would play at the young end of the lifespan, the current approach better served the long-term goal of determining whether ERPs measured during executive functioning can effectively serve an adjuvant role to ε4 and neuropsychological testing in improving diagnosis and prediction of cognitive decline, or in identifying who to target for early intervention. Indeed, as *APOE* ε4 inheritance alone is not sufficient to predict cognitive decline (e.g., [1, 15]), our findings suggest ERPs during a stop-signal task could improve prediction. Future study including a lifespan perspective of ε4 effects could add to these findings.

Notably, our approach was designed to maximize task accuracy over SSRT precision [89], in order to best compare young and old while limiting contributions of task difficulty. Although SSRT values were consistent with other studies suggesting little effect of this approach on outcomes, future studies allowing for a more equivalent number of accurate and error trials might add to our understanding of both age and ε4 effects in stop-signal tasks. Indeed, given the high functioning of the current sample, examination of error trials might have afforded more group differentiation across tasks, if the influence of task difficulty and increased task length could be effectively mitigated or measured. Finally, somewhat greater range in cognitive functioning of the sample would be valuable to provide more ecological validity.

CONCLUSION

The present study highlights age-related ERP changes that are consistent with the general cognitive aging literature. Specifically, despite comparable task accuracy across groups, N200 and P300 latencies evidenced age-related slowing and generally reduced amplitude in older versus young adults. The frontal electrodes were an exception, where there was evidence of increased amplitude in older adults. Increased anterior amplitude is consistent with compensatory models [37–39], suggesting there was recruitment, particularly of frontal resources, in cognitively intact older adults during executive functioning. Moreover, in the stop-signal task, greater N200 amplitude at frontal and central sites was attributable specifically to the *APOE* ε4+ participants. Since these neural activity differences were seen in the ab-sence of task performance or neuropsychological differences from ε4- participants, electrophysiological measures may be more sensitive than neuropsychological testing to early changes associated with risk for AD. Significantly prolonged latency of the N200 and P300 ERPs, but no amplitude differences, have previously been reported among cognitively intact elders at risk for AD using oddball paradigms [81–83]. The present study suggests that compensatory mechanisms may be better elicited by more complex executive functioning tasks, particularly the stop-signal paradigm, and highlights the potential importance of N200 amplitude during stop-signal tasks as a novel, early indicator of risk for AD risk. Finally, these results underscore the need for more investigation of cognitive domains other than memory when exploring risk factors for AD, and the value of specifically

examining executive abilities, and inhibition specifically, as preclinical markers of risk for cognitive decline and dementia.

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