A Behavioral and Neural Investigation of the Impact of Age and Genetic Risk for Alzheimer's Disease on Inhibitory Control

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A BEHAVIORAL AND NEURAL INVESTIGATION OF THE IMPACT OF AGE AND GENETIC RISK FOR ALZHEIMER'S DISEASE ON INHIBITORY CONTROL

by

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ABSTRACT
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Significant advances have been made in understanding Alzheimer's disease (AD), but our ability to accurately predict who will develop AD remains limited. Executive functioning has been neglected as a preclinical marker of AD, despite the vital role of these abilities (e.g., planning, set shifting, inhibition) in everyday functioning. Inhibitory deficits in particular have been found to predict impairment in activities of daily living, an important criterion in the diagnosis of AD.

This study examined differences in behavioral task performance and underlying neural processing based on event related potentials (ERPs) during an inhibition task as a function of age and genetic risk for AD based on apolipoprotein-E (APOE) ε4 status. Participants included 49 healthy, cognitively intact older adults and 42 young adult college students. Genetic testing was conducted for older adults, 24 of whom were APOE ε4 carriers. Participants completed the Parametric Go/NoGo/Stop (PGNGS) task while EEG data was collected for later extraction of ERPs.

Significant ERP differences by genetic risk emerged such that APOE ε4+ participants exhibited significantly more negative amplitudes than APOE ε4- participants at midline electrodes in response to Stop trials (Fz: $p<.001$, FCz: $p=.002$, Cz: $p=.012$). These neural differences were seen in the absence of genetic risk differences in behavioral task performance, suggesting that psychophysiological measures may be more sensitive to early disease stage differences than neuropsychological testing alone. Expected age differences also emerged, with older adults exhibiting slower response times and longer ERP latencies in most task conditions and at most electrode sites.

In conclusion, this study revealed significant ERP differences across genetic risk groups in cognitive intact older adults, revealing a new early marker of AD risk. Moreover, these findings underscore the importance of considering executive abilities, such as inhibition, as preclinical markers of risk for AD.

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A BEHAVIORAL AND NEURAL INVESTIGATION OF THE IMPACT OF AGE AND GENETIC RISK FOR ALZHEIMER'S DISEASE ON INHIBITORY CONTROL

Despite significant advances in our understanding of cognitive changes that occur with advancing age and in those with Alzheimer's disease (AD), our ability to accurately predict who will remain cognitively intact and who will develop AD remains limited. In order to improve this prediction and early detection of AD, research is expanding in many directions through utilization of a variety of methodologies for studying those with, and at risk for, AD (i.e., neuroimaging, electrophysiological measures, neuropsychological testing) as well as by exploring domains of cognition beyond memory, which has long been considered the hallmark domain of cognitive impairment in AD. Executive functioning is one such cognitive domain that has been largely neglected as a preclinical marker of AD, despite the vital role of executive abilities (e.g., planning, set shifting, inhibition) in everyday functioning. Further exploration of the ways in which executive functioning changes with age and as a function of risk for, or development of, AD is needed to expand the scope of cognitive and neural markers of AD and improve the likelihood of early detection and prevention.

Executive Functioning and its Role in Aging and AD

Executive functioning is an umbrella term used to describe higher order cognitive processes that are critical for engagement in complex thought and behavior (Daniels, Toth, & Jacoby, 2006; Elliott, 2003). Executive functioning includes abilities such as planning, shifting from one mental set to another, updating and monitoring of information, and inhibitory control (Miyake et al., 2000). Individuals with AD have been

shown to exhibit poorer performance than healthy controls on a variety of executive tasks, such as those assessing the ability to divide attentional resources, manipulate information in working memory, capacity to inhibit a habitual response, and monitoring of self-generated responses (Collette, Van der Linden, & Salmon, 1999). These executive skills are critical for effectively navigating one's daily life throughout the lifespan and, specifically, for completing activities of daily living (ADLs), which become an area of increasing concern in old age and dementia. The importance of considering the role of executive functioning in ADLs should not be understated given that the differentiation between dementia and earlier stages of disease progression (e.g., mild cognitive impairment) relies heavily on assessing one's ability, or lack there off, to independently complete ADLs
(Alzheimer's Association, 2013; Alzheimer's Association, 2015).

ADLs include complex (also known as instrumental) skills such as managing medications, managing finances, shopping, and preparing meals as well as more basic skills such as feeding, toileting, bathing, and dressing. Numerous studies have linked executive functioning deficits to declining ability to complete ADLs (Back-Madruga et al., 2002; Royall, Palmer, Chiodo, & Polk, 2004). Additionally, among individuals with AD, executive functioning may play a larger role in determining functional ability than another other cognitive domain, including memory (O'Connor & Boyle, 2007). One study assessing executive abilities in patients with AD found that 64% of patients exhibited executive deficits, with this group performing worse on a measure of global cognitive impairment, exhibiting greater dementia severity, and displaying poorer scores on a measure of ADLs than patients with normal executive functioning abilities

(Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). Additionally, executive functioning deficits tend to occur early in the course of AD disease progression. In a prospective study of 551 individuals who were cognitively intact at baseline, individuals who converted to AD 1.5 years later showed the greatest magnitude of decline on measures of executive functioning in addition to memory (Chen et al., 2001).

Structural changes occurring in the brain throughout the process of aging and among individuals with dementia also speak to the importance of focusing on executive functioning. Among healthy older adults, reductions in grey matter volume are most pronounced in frontal and parietal regions (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Volumetric decreases in prefrontal cortex (PFC) begin as early as age 20 and continue throughout adulthood at a rate of 5% per decade (Hedden & Gabrieli, 2004). This pattern of frontal grey matter degradation is consistent with executive functioning deficits given the role of the PFC in executive control (Miller & Cohen, 2001). While grey matter loss in AD is typically most pronounced in the temporal cortex, particularly in the medial temporal lobe (MTL), hippocampus, entorhinal cortex, and parahippocampal gyrus (Ohnishi, Matsuda, Tabira, Asada, & Uno, 2001; Uylings & de Brabander, 2002), frontal lobe changes are apparent in these patients as well. Localization of PFC volume decline varies among older adult groups, with the most significant decline occurring in the lateral PFC among healthy older adults (Tisserand et al., 2002) and the inferior PFC among AD patients (Salat, Kaye, & Janowsky, 2001). The inferior frontal region has been specifically implicated in cognitive control and EF deficits in patients with AD (Schroeter et al., 2012).

White matter pathways, which allow for communication between brain regions, also become compromised with age (Goh & Park, 2009). Such white matter degradation is evident even among very healthy older adults, particularly in prefrontal regions (Raz et al., 2005; Resnick et al., 2003). Decreased communication between frontal and striatal regions as a result of white matter deficiency leads to executive deficits (Buckner, 2004; Head et al., 2004). Additionally, memory deficits may be linked to the executive dysfunction that results from fronto-striatal disruption due to higher order executive processing being necessary for effective encoding and retrieval of information (Buckner, 2004).

Inhibition as a Specific Executive Function of Interest

Inhibition is one specific component of the larger set of executive abilities that has been show to decline with age and in the context of AD. Moreover, inhibitory deficits specifically may underlie age-related changes in cognitive ability (Hasher, Lustig, & Zacks, 2007; Hasher & Zacks, 1988; but see also Salthouse, 1996a; Salthouse, 1996b, 2005; Verhaeghen, 2011) and have been shown to predict impairment in the ability to complete ADLs (Jefferson, Paul, Ozonoff, & Cohen, 2006).

Hasher and Zacks proposed a theory specifically related to the executive ability of inhibition, which has been broadly applied in the contexts of memory, comprehension, and attention (Hasher et al., 2007; Hasher & Zacks, 1988). Within this framework, cognitive functioning relies on the combination of excitatory and inhibitory processes, with age-related deficits being driven by failures of the inhibitory, but not excitatory, mechanisms (Zacks & Hasher, 1997). Applied in the context of memory, diminished inhibitory abilities lead to greater amounts of irrelevant information being allowed into

working memory, this irrelevant information becoming a focus of sustained activation, and this misguided focus resulting in poorer initial encoding of target information and greater competition between ideas at retrieval. Patterns of cognitive functioning in older adults are consistent with this view as evidenced by inhibitory decrements that result in increased intrusions rates during free recall and false positives during recognition (Hasher & Zacks, 1988).

According to this theory, three specific inhibitory processes underlie the functioning of this overall inhibitory mechanism: (1) access, (2) deletion, and (3) restraint (Hasher et al., 2007; Hasher & Zacks, 1988; Hasher, Zacks, & May, 1999; Lustig, Hasher, & Zacks, 2007). The access component is responsible for determining the critical information that requires access to attention and suppressing irrelevant information that should be restricted from access to consciousness. Deletion serves to remove irrelevant information that has become the focus of attention via failure of the access process. Additionally, it is through the process of deletion that previously relevant information that has now become irrelevant is removed from the focus of attention. Finally, restraint involves the control of strong responses, which can be related to both thought and behavior (e.g., an automatic thought, a prepotent motor response). Evidence suggests that the access, deletion, and restraint mechanisms are weakened with increasing age such that older adults, compared to young adults, are less selective in the amount of information they generate and place attentional focus on (i.e., access), slower to respond when extraneous stimuli are presented due to decreased ability to limit task focus to relevant information (i.e., deletion of irrelevant information), and have greater difficulty withholding strong responses (i.e., restraint) (Hasher et al., 2007).

Neuropsychological testing to evaluate inhibitory control (i.e., the ability to withhold a prepotent response) is commonly conducted using Go/No-Go and Stop Signal tasks (Congdon et al., 2012) in which subjects respond to Go stimuli, while withholding responses to No-Go stimuli or target stimuli that are interrupted with a stop signal (i.e., Stop stimuli). In Go/No-Go tasks, the primary trials of interest are correct rejection trials, in which subjects accurately inhibit their response to No-Go stimuli, and commission trials, in which subjects fail to inhibit this response (Congdon et al., 2012; Simmonds, Pekar, & Mostofsky, 2008).

Nielson, Langenecker, and Garavan (2002) utilized a Go/No-Go task to compare participants in four age groups ranging from young adults to elderly adults and found that increased age was associated with decreases in inhibitory performance. In the context of risk for AD, a study utilizing the Frontal Assessment Battery (Dubois, Slachevsky, Litvan, & Pillon, 2000) found that declines in Go/No-Go performance corresponded with disease progression such that patients with AD performed worse than patients with mild cognitive impairment, who in turn performed worse than health controls (Hanyu, Sato, Takasaki, Akai, & Iwamoto, 2009).

While reactions times can be easily obtained on commission trials, successful inhibition presents a more complex measurement issue given its covert nature since there is no reaction time for the lack of a response. When considering the possible metrics that can be used to assess behavioral performance, this is a limiting factor for standard Go/No-Go tasks. However, Stop Signal tasks are specifically designed to account for this and provide a measure of reaction time for successfully inhibited trials (Band & van Boxtel, 1999; Logan, 1994).

The theoretical framework for the stop signal paradigm is based on the horse-race model positing that competing "go" and "stop" processes are in a race that determines whether a response is executed or inhibited (Congdon et al., 2012; Logan, 1994; Logan & Cowan, 1984). If the "go" process finishes before the "stop" process, the response is executed; if the "stop" process finishes before the "go" process, the response is inhibited. The latency of the internal stop process, a metric known as the Stop Signal Reaction Time (SSRT), can be calculated based on when the stop signal is presented (stop signal delay, SSD) and the time at which the internal stopping process is complete (Logan, 1994). Practically speaking, this latter component is computed using the distribution of the reaction times to Go trials and frequency of inhibitory errors on Stop trials to quantify the time needed for the response to be inhibited after seeing the stop signal, with small SSRTs indicating greater inhibitory efficiency and larger SSRTs indicating poorer inhibitory functioning (Chao, Luo, Chang, & Li, 2009; Hirose et al., 2012).

Studies assessing Stop Signal task performance across the lifespan have found that the ability to inhibit a response in the face of a stop signal increases throughout childhood before diminishing in adulthood, with older adults exhibiting significantly greater SSRTs than young adults (Bedard et al., 2002; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). A study comparing healthy older adults and those with AD revealed a trend toward poorer stop signal performance among AD patients. Also, a greater proportion of individuals with AD, compared to healthy controls, committed at least one stop trial inhibition error (Amieva et al., 2002).

ERPs as a Measure of Neural Functioning in Aging and AD

As research on aging and AD is increasingly focused on assessment of the neural underpinnings of cognitive functioning, it is important to extend our work beyond an examination of behavioral performance and garner more direct measures of brain activity itself. One significant obstacle in these pursuits is often the substantial expense associated with using neuroimaging methodologies, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Alternatively, electroencephalography is a less expensive and less invasive modality for assessing neural function. Event-related potentials, which reflect coordinated neural activity in response to sensory, cognitive, or motor processes, can be extracted from the neural signal to assess cortical function (Bressler, 2002; Falkenstein, Hoormann, & Hohnsbein, 1999).

Electroencephalography is an electrophysiological approach that has been used to study inhibitory control. Using electroencephalography, neural activity is recorded by placing electrodes on the scalp and connecting them to an amplifier that records changes in the voltage of electrical signal produced by populations of cortical neurons (Coles & Rugg, 1995). These voltage fluctuations across the scalp are referred to as the electroencephalogram (EEG). The EEG signal produces a sinusoidal waveform with repetitive cycles that are measured as a function of amplitude and frequency (Hugdahl, 1995). Amplitude is the magnitude of change in electrical signal measured in microvolts (μV), while frequency is the number of cycles occurring per second measured in hertz (Hz).

When particular stimuli are of interest, time epochs surrounding those stimuli can be isolated and the data within those epochs then averaged to reduce the noise and reveal

voltage changes reflecting the neural response to those specific stimuli. The voltage changes occurring during those epochs are referred to as event-related potentials (ERPs; also known as evoked potentials) (Coles & Rugg, 1995). Use of this type of methodology is particularly advantageous when studying a topic such as inhibition given its ability to provide insight into real-time neural processing of stimuli even when no behavioral response occurs (e.g., in the case of successful inhibition).

ERPs are described using a specific nomenclature that contains both a polarity and temporal property. For example, ERP labels such as P300 and N200 (often abbreviated to P3 and N2, respectively) are commonly used to describe peaks in the EEG waveform. These labels refer to the signal polarity (P = positive, N = negative) and approximate latency post stimulus presentation (in milliseconds) at which they occur in the waveform (Luck, 2005). Numerous other factors can be considered when making inferences about cognitive function based on ERPs. For example, interferences about the variation in neural response to Go stimuli versus No-Go stimuli could be determined by evaluating differences in the ERP waveforms elicited by the two stimulus types, which can be driven by differences in the timing at which the waveforms begin to differ, the latency at which various ERP components appear following the eliciting event, the spatial distribution of ERPs across all electrode sites, and the amplitude of ERPs (Coles & Rugg, 1995). It is important to note that the interpretation of various ERPs and waveform features is dependent on the specific paradigm utilized to elicit the neural response.

ERPs can be classified into early potentials reflecting automatic, and often sensory-related, processing and later potentials reflecting controlled and often higher-order cognitive processing (Hugdahl, 1995). One early ERP, P50, was recently identified

as a potential ERP biomarker of prodromal AD based on a study finding that P50 amplitudes were greater among amyloid-positive (a marker of AD pathology), compared to amyloid-negative, patients with mild cognitive impairment (Green et al., 2015). This ERP, which occurs in response to auditory stimuli and is generated in auditory cortices, has been linked to inhibitory processing. Its amplitude is believed to be mediated by frontal regions of the brain and reflects a process known as sensory gating, or the inhibition of irrelevant stimuli at the stage of early sensory processing (Boutros & Belger, 1999; Green et al., 2015). This evidence that inhibition at the sensory level may serve as a marker of AD pathology, along with previous research suggesting that later ERP components reflecting controlled processing (e.g., N2, P3) are more sensitive to dementia than early sensory components (Olichney, Yang, Taylor, & Kutas, 2011), begs the question of how neural markers of inhibition in the context of higher-order cognitive processing may add further predictive value.

Previous research examining ERPs in Go/No-Go and Stop Signal tasks has been predominantly focused on N2, an ERP typically following improbable or deviant events that occur less often throughout a task, such as No-Go trials (Coles & Rugg, 1995; Luck, 2005; Mathalon, Whitfield, & Ford, 2003), and P3, which reflects information processing when attention and memory mechanisms are engaged (Polich, 2007). N2 ERPs elicited by correct rejections to No-Go trials have been described as a frontally maximum negativity, with decreasing amplitude from frontal to occipital regions (Falkenstein et al., 1999). Significant variations in the P3 across stimulus types (Go, No-Go, Stop) have been found, with P3 activations being higher in inhibitory trials than non-inhibitory trials (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010). A study examining localization of

the P3 found that this ERP was comparable for Go and No-Go trials at parietal electrodes, though it was larger for No-Go trials at central and frontal electrodes as would be expected based on the role of frontal brain regions in inhibitory control (van Boxtel, van der Molen, Jennings, & Brunia, 2001).

Studies examining the effects of age on N2 and P3 ERPs have shown significant differences in these ERPS across the lifespan. In one study assessing children, adolescents, young adults, and older adults, a linear decrease in N2 amplitudes was seen in both Go and NoGo conditions, with a steeper decrease in the NoGo condition (Hämmerer, Li, Muller, & Lindenberger, 2010). Another study examining response during a Go/NoGo task in young adult and elderly participants found smaller amplitudes and longer latencies for N2 as well as longer latencies for P3 in the elderly group (Falkenstein, Hoormann, & Hohnsbein, 2002). Mixed results have been reported regarding the effect of age on P3 amplitudes, with evidence emerging of both reduced (Hämmerer et al., 2010) and increased (Vallesi, 2011) P3 amplitudes in older adults.

Variations in the N2 and P3 ERPs are also evident among patients with AD. Studies assessing these ERPs among AD patients have typically utilized oddball paradigms in which auditory or visual stimuli evoke neural response to unpredictable target events that occur infrequently amongst frequent standard events (Herrmann & Knight, 2001). Patients with AD exhibit prolonged P3 latency to auditory stimuli and smaller P3 amplitude to visual stimuli (Pokryszko-Dragan, Slotwinski, & Podemski, 2003). P3 latencies up to 2 standard deviations slower than those of healthy older adults have been seen in patients with AD (Olichney et al., 2011). Similar findings have emerged in examining individuals with amnestic mild cognitive impairment, a significant

risk factor for later development of AD. In one such study, participants with amnestic mild cognitive impairment exhibited smaller N2 amplitudes than healthy controls, while P3 amplitudes and N2 and P3 latencies did not differ across groups (Cid-Fernandez, Lindin, & Diaz, 2014). These findings underscore the importance of examining groups at risk for AD in addition to studying those who have already developed the disease.

Risk for AD and the Study of Preclinical Populations

Early detection, and ideally prevention and treatment, of AD requires research focused on earlier stages of AD disease progression. Impairment in the symptomatic, but 'predementia,' stage of AD is commonly referred to as mild cognitive impairment (MCI) and involves changes in cognition marked by impairment in one or more cognitive domains, with preserved ability to complete ADLs independently (Albert et al., 2011) The differentiation of AD and MCI is based largely on this latter criterion regarding impairment, or lack thereof, in completing ADLs (Albert et al., 2011; American Psychiatric Association, 2013; McKhann et al., 2011). Given research evidence suggesting that AD pathophysiology begins years, and possibly even decades, before the onset of clinical symptoms (Twamley, Ropacki, & Bondi, 2006), focus is now also shifting to identification of even earlier preclinical, presymptomatic stages of AD (Sperling et al., 2011). According to Sperling et al. (2011), identification of preclinical AD focuses on the presentation of a number of AD biomarkers, including (and typically emerging in this order) cerebral amyloidosis in the form of amyloid-β (Aβ) protein accumulation, synaptic dysfunction and/or neurodegeneration, and subtle cognitive deficits that would not meet criteria for MCI.

Though there is no perfect formula at present for identifying individuals who will go on to develop AD, certain factors offer insight into who may be more likely to do so. One such factor is genetic risk for AD. According to the Alzheimer's Association (2015), the apolipoprotein-E (APOE) gene, and specifically the ε4 allele, is among the top risk factors for AD. The APOE gene is related to amyloid deposition and neurofibrillary tangles formation in the brain (Twamley et al., 2006). Individuals inherit one of three APOE alleles (ε2, ε3, ε4) from each of their parents, with the different alleles carrying differing levels of risk for AD. While the APOE ε3 allele (the most common form of the APOE gene) is believed to have minimal positive or negative impact, APOE ε2 may have a protective effect and even minimize risk for AD, while APOE ε4 has been identified as carrying increased risk of developing AD and causing onset to occur at a younger age (Alzheimer's Association, 2015).

Being an APOE ε4 carrier does not guarantee the development of AD; however, the presence of the APOE ε4 allele is disproportionate among patients with AD compared to nondemented individuals, occurring in 40-65% of individuals in the former group and only 16% of individuals in the latter group (Alzheimer's Association, 2013; Twamley et al., 2006). Because all individuals possess two APOE alleles, APOE ε4 carriers are either heterozygotes (carrying one ε4 allele and either an ε2 or ε3 allele) or homozygotes (carrying two ε4 alleles). The likelihood of AD development increases with the number of ε4 alleles an individual possesses. Compared to APOE ε4 non-carriers, heterozygote APOE ε4 carriers have a 3 times greater chance of developing AD, while homozygote APOE ε4 carriers have a 15 times greater chance (Twamley et al., 2006).

Family history of AD is an additional risk factor for disease development that is not

completely accounted for by the genetic risk associated with APOE ε4 (Alzheimer's Association, 2015). Having a first-degree relative with AD has been linked to greater risk of an individual developing the disease, with that risk growing as the number of afflicted first-degree relatives increases. The exact mechanisms underlying familial risk for AD are not entirely known but are likely to be a combination of genetics, shared environment, and lifestyle factors (Alzheimer's Association, 2015).

Of the work that has been conducted regarding inhibition in AD, relatively minimal attention has been paid to examining individuals at early, preclinical stages of disease progression, such as in healthy individuals at risk for AD. However, promising findings have emerged in the limited research that has been conducted in this area. In the context of risk by family history, cognitively intact older adults with a family history of AD have been shown to perform more poorly on the Wisconsin Card Sorting Test, a classic measure of executive functioning (Grant & Berg, 1948; Heaton, 1981; Heaton, Chelune, Talley, Kay, & Curtis, 1993), than individuals without a family history of AD (Hazlett, Figueroa, & Nielson, 2015). To date, we are aware of only one study (Wetter et al., 2005) that has behaviorally examined the link between APOE ε4 inheritance and inhibition. Wetter et al. (2005) examined response inhibition and cognitive switching in cognitively intact APOE ε4 carriers and non-carriers using the Color-Word Interference Test of the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001). Results indicated a significantly greater error rate in the Inhibition/Switching condition, more heterogeneous error-rate variability, and a greater correlation between error rate and cognitive status among APOE ε4 carriers.

In the context of ERP research, genetic risk factors have been linked to N2

amplitude in auditory oddball paradigms. Among individuals with MCI, APOE ε4 carriers have been show to exhibit attenuated N2 amplitude compared to non-carriers, with a gene-dose relationship emerging in correlations between N2 amplitude and the number of APOE ε4 alleles, such that amplitude attenuation was associated with a greater number of ε4 alleles (Reinvang, Espeseth, & Gjerstad, 2005). Significantly prolonged latencies of the N2 and P3 ERPs have also been found among cognitively intact individuals with familial and genetic risk for AD (Green & Levey, 1999). These ERP differences were evident in comparison to individuals without family history of AD despite a lack of difference between groups on neuropsychological measures, suggesting that electrophysiological measures may be more sensitive to early disease stage differences than neuropsychological testing alone. Another study examining individuals with genetic factors (presenilin and amyloid-precursor protein) causing autosomal dominantly inherited familial AD (FAD) found that the FAD mutation carriers had significantly longer N2 and P3 latencies in response to an oddball task (Golob et al., 2009). Extrapolation of these oddball paradigm findings to Go/No-Go and Stop Signal tasks may further elucidate the relationship between risk factors such as APOE ε4 inheritance and executive abilities such as inhibition. Moreover, additional research examining these constructs in individuals *at-risk,* but not yet exhibiting cognitive decline, is needed for better understanding of early disease progression.

The Present Study

The present study examined differences in behavioral task performance and ERPs elicited during a Go/No-Go/Stop task, with a specific focus on age- and genetic risk-related differences in a cognitively intact sample.

Hypotheses

This study first sought to examine differences in behavioral task performance, as measured by accuracy and reaction time variables, across age and genetic risk groups in the Go, Stop, and NoGo conditions. The following hypotheses were posed:

1. Age group effects:
    A. Based on past literature suggesting declines in inhibitory functioning with age (Nielson et al., 2002), it was expected that young and older adults would not differ in their accuracy in responding to targets in the Go condition (Percent Correct Target Trials; PCTT), but that older adults would exhibit poorer accuracy than young adults on inhibitory trials in the Stop and NoGo conditions (Percent Correct Inhibitory Trials; PCIT).
    B. Based on substantial past literature indicating decreases in processing speed with age (Salthouse, 1996b, 2005), it was predicted that older adults would exhibit slower reaction times across all conditions. Specifically, older adults were expected to exhibit slower Response Times to Target trials (RTT) in the Go condition and slower Stop Signal Reaction Times (SSRT) in the Stop condition compared to young adults. (No reaction time measure was assessed in the NoGo condition, as reaction times cannot be calculated for inhibitory trials in this condition).
2. Genetic risk group effects:
    A. Although the previously mentioned study by Wetter et al. (2005)

indicated significant risk group differences in the Inhibition/Switching condition of the DKEFS CWIT and no such differences in the Inhibition only condition, the difficulty of the inhibitory control task utilized in the present study likely falls between that of these two conditions and may be more sensitive to genetic risk differences than the CWIT Inhibition Only condition. Thus, it was expected that genetic risk group differences in accuracy on inhibitory trials (PCIT) would emerge, such that the APOE ε4+ elders would exhibit poorer inhibition than the APOE ε4- elders in the Stop and NoGo conditions. No significant differences in target trial accuracy (PCTT) were expected.

B. Regarding genetic risk differences in reaction time, we hypothesized that Reaction Time to Targets in the Go condition (RTT) would not differ across groups, while reactions times to stop signal trials (SSRT), which have an inherent inhibitory component, would be slower in the APOE ε4+ elders than the APOE ε4- elders due to poorer overall inhibitory functioning.

The second goal of this study was to examine the neural activity (i.e., ERPs) associated with Go, Stop, and No-Go task performance in order to assess the degree to which ERPs are sensitive to group differences, perhaps above and beyond behavioral test results. This is particularly novel with regard to genetic risk as this type of ERP study examining inhibition in individuals at genetic risk for AD has not been previously conducted. Hypotheses regarding differences in ERPs, specifically N2 and P3, are based on findings from only somewhat comparable paradigms (e.g., oddball paradigms) and

ERP studies assessing inhibition among individuals who have already reached AD onset. Assessing the ways in which these ERPs manifest themselves during an inhibitory control task in cognitively intact elders with varying degrees of genetic risk for AD, as well as across two different age groups, significantly adds to the literature and our understanding of the neural basis of inhibition. Additionally, examination of ERP differences at this early stage of risk may help to improve prediction of who will go on to develop AD. To assess these ERP differences, latency and amplitudes of the N2 and P3 ERPs during correct hits for target trials in the Go condition (Go trials) and correctly rejected inhibitory trials in the Stop (Stop trials) and NoGo (NoGo trials) conditions were extracted and compared across groups.

3. Age group effects:
    A. We hypothesized that older adults would have longer N2 and P3 latencies and smaller N2 and P3 amplitudes compared to young adults for Go, Stop, and NoGo trials. We expected differences in Stop and NoGo trials, in particular, to be most significant at frontal electrode sites given the executive functioning demands of these task conditions.
4. Genetic risk group effects:
    A. We hypothesized that APOE ε4+ elders would have longer N2 and P3 latencies and smaller N2 and P3 amplitudes compared to APOE ε4- elders for Go, Stop, and NoGo trials. Again, we expected differences in Stop and NoGo trials, in particular, to be most significant at frontal electrode sites given the executive functioning demands of these task conditions.

Method

Participants

Forty-nine older adults and 42 young adults participated in the present study. Older adult participants were initially recruited from the local community via newspaper advertisements emphasizing participation of healthy participants with a family member diagnosed with AD. This was done to increase the likelihood of obtaining a balanced sample with regard to genetic risk groups given that the base rate of APOE ε4 positive gene status is higher among those with a family history of AD than in the general population (Huang, Qiu, von Strauss, Winblad, & Fratiglioni, 2004). The sample for the present study included 24 APOE ε4 positive (APOE ε4+) and 25 APOE ε4 negative (APOE ε4 -) participants. Young adult participants were undergraduate students who volunteered to participate through the Psychology Subject Pool.

Measures

Parametric Go/NoGo/Stop Task (PGNGS). The PGNGS task is based on the Parametric Go/No-Go task (PGNGS; Langenecker, Zubieta, Young, Akil, & Nielson, 2007) with an additional Stop Signal condition. The PGNGS consists of 3 conditions, presented in the following order: Go, Stop, and No-Go (Figure 1). In all 3 conditions, a serial stream of letters is presented in black ink against a light grey background on a computer screen at a rate of 750 ms per letter with an interstimulus interval of 0 ms.

In the Go condition, participants are instructed to press the space bar each time the letters “r” and “s” are presented. This condition serves to establish the prepotent motor response to “r” and “s” targets and to evaluate attention and psychomotor speed. In the following Stop condition, participants are instructed to press the space bar each time

the letters “r” and “s” appear *unless the stimulus is interrupted by a stop signal*. The stop signal is a red screen that briefly flashes for 100 ms either 125 ms or 200 ms after the letter appears. In the No-Go condition, participants are instructed to press the space bar each time the letters “r” and “s” appear *in alternation*. The participant should never respond to the same target letter twice in a row. The Stop and No-Go conditions assess inhibitory control; participants must inhibit the proponent tendency to respond to an “r” or an “s” under specific, newly defined conditions.

For each of the 3 task conditions, 2 blocks of practice trials were completed prior to beginning the test blocks. During the first practice block, stimuli were presented at a rate of 1000ms per stimulus to help participants become acquainted with the task instructions. Stimuli in the second practice block were presented at the same speed as the actual test blocks. These two practice blocks provided an opportunity for incremental acclimation to the task demands.

To reduce the potential for fatigue during task completion, each testing block was separated into 3 parts by rest breaks. Each rest break lasted for 20 seconds, during which participants were briefly reminded of the task instructions and told that the task would resume in a few seconds.

Mattis Dementia Rating Scale - Second Edition (DRS-2). The DRS-2 (Jurica, Leitten, & Mattis, 2001; Mattis, 1988) is a measure of cognitive status assessing five domains of cognitive ability: attention, initiation/perseveration, construction, conceptualization, and memory. The total DRS-2 score was used in the present study to screen for cognitive impairment among the older adult sample. A cut-off score of 130

was used as a marker of intact cognitive ability based on prior literature (Monsch et al., 1995).

EEG data acquisition and event-related potentials. EEG data were collected using a 64-channel active electrode actiCAP (Brain Products) and recorded using Neuroscan SynAmps2 with impedances kept under 50 kΩ. Electrodes on the actiCAP were arranged according to the extended international 10-20 system with a reference at FCz and a ground at AFz (Figure 2). Based on this system, the distance between adjacent electrodes is either 10% or 20% of the total distance from the front to the back (i.e., nasion to inion) or right to the left (i.e., right to left preauricular points anterior to the ear) of the skull (Trans Cranial Technologies, 2012). The EEG was recorded continuously in DC mode with a low-pass hardware filter at 100 Hz and a 500 Hz sampling rate using Neuroscan software (Scan 4.5).

EEG data were processed off-line using MATLAB (version 7.12, The MathWorks) for extraction of ERPs. After converting the raw Neuroscan data (.cnt) files to set files (.set) and loading the electrode cap locations, the continuous 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.

Data were examined and artifact noise was rejected at the channel, component, and epoch level of data processing. First, data for individual channels (i.e., electrodes) were examined and rejected based on visual inspection. Data for rejected channels were interpolated based on the response at surrounding channels. Next, an Adaptive Mixture Independent Component Analysis (AMICA; Palmer, Makeig, Kreutz-Delgado, & Rao,

2008) was used to decompose signals for each trial into 64 individual components. Component rejection, particularly to remove artifacts reflecting ocular movements and muscle contraction, was conducted based on visual data inspection. The data were then epoched around specific stimuli of interest. Epochs for Go and NoGo trials were defined as 100 ms prior to stimulus onset (e.g., presentation of the letter) to 1500 ms after stimulus onset. The same epoch range of 100ms pre to 1500 ms post was used for Stop Signal trials; however, these epochs were averaged around the stop signal presentation (e.g., the red flash). Again, epochs were examined and rejected as appropriate based on visual inspection. Remaining epochs were averaged to reduce noise and baseline corrected using the mean of the 100 ms pre-stimulus interval. Finally, additional low-pass filtering of the EEG data eliminated extraneous noise above 20hz (zero-phase, 4^{th}-order, Butterworth).

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 N2 and 300 and 700 ms for P3. These electrode sites and latency periods were selected based on an extensive review of the literature regarding N2 and P3 ERPs in the context of inhibitory control (Brydges et al., 2012; Cid-Fernandez et al., 2014; Enriquez-Geppert et al., 2010; Falkenstein et al., 1999, 2002; Golob et al., 2009; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Pires, Leitao, Guerrini, & Simoes, 2014; Roche, Garavan, Foxe, & O'Mara, 2005; Upton, Enticott, Croft, Cooper, & Fitzgerald, 2010).

Procedure

Participants completed two testing sessions, approximately 1 week apart. Participants were tested individually at both sessions and the informed consent process

was completed at the beginning of each session. The first session included completion of neuropsychological testing, including the DRS-2 to screen for cognitive impairment. Additionally, head measurements were taken at the end of the first session to determine which EEG cap would be used at the second session.

During the second session, EEG data were collected during completion of 4 cognitive tasks, including the PGNGS task. The order in which these tasks were completed varied across participants and was determined based on a Latin squares design. Participants were briefly oriented to the EEG procedures at the start of the session. They then completed questionnaires while the EEG cap, with inset scalp electrodes, was placed on their head and conductive gel was inserted into each of the electrodes using a blunt tip needle to facilitate acquisition of the neural signal from the scalp. This process took approximately 20 minutes to complete.

Participants were situated in front of a computer, on which the cognitive tasks were presented, and instructed to limit gross motor movements as much as possible to reduce noise in the EEG signal. The PGNGS task was presented in MATLAB (version 7.12, The MathWorks). PGNGS instructions were read aloud to participants as they appeared on the screen and questions regarding task instructions were answered as needed in an attempt to ensure understanding of the task instructions. Corrective feedback was provided as needed throughout the practice blocks of each task condition. No feedback was provided during the actual test blocks of the task.

Older adult participants were compensated monetarily for their involvement in the study while young adults were compensated with course credit. All procedures were approved by the Marquette University Institutional Review Board.

Results

Excluded and Missing Data

One older adult participant (APOE ε4+) was excluded from all analyses due to a DRS-2 score of 121, which feel below the cut-off for intact cognitive ability. This resulted in a final sample of 48 older adults (23 APOE ε4+, 25 APOE ε4-) and 42 young adults. Sample demographics are presented in Table 1. Age groups did not significantly differ by education or sex. Genetic risk groups did not significantly differ with regard to sex or scores on the DRS-2; however, the APOE ε4+ group had more years of education than the APOE ε4- group. Given that this difference was in the direction of a protective effect for the high-risk group, which would be expected to attenuate rather than accentuate any of our hypothesized group differences if it did have any effect (Sharp & Gatz, 2011), education was not included as a covariate in our statistical analyses.

Of the final 90 participants included in the sample, select participants were excluded from certain analyses for the following reasons. Two older adults (both APOE ε4+) were excluded from all Stop condition analyses due to extremely poor performance and a pattern of responses indicating a lack of understanding of this task condition. Software errors during data acquisition resulted in missing behavioral data in the Go condition for 1 older adult participant (APOE ε4-) and missing ERP data for select conditions in 7 participants. Specifically, ERP data were missing for 3 older adults (2 APOE ε4-, 1 APOE ε4+) and 1 young adult in the Go condition, for 2 older adults (both APOE ε4 +) in the Stop condition, and for 1 older adult (APOE ε4-) and 1 younger adult in the NoGo condition.

To maximize the statistical power of the analyses conducted, each analysis

included the maximum number of participants possible, resulting in slight differences in sample size across analyses. Exact sample sizes were as follows. Behavioral analyses included 42 younger adults in all conditions and 47 (23 APOE ε4+, 24 APOE ε4-), 46 (21 APOE ε4+, 25 APOE ε4-), and 48 (23 APOE ε4+, 25 APOE ε4-) older adults in the Go, Stop, and NoGo conditions, respectively. ERP analyses included 41 young adults in the Go and NoGo conditions and 42 young adults in the Stop condition, with 45 (22 APOE ε4+, 23 APOE ε4-), 46 (21 APOE ε4+, 25 APOE ε4-), and 47 (22 APOE ε4+, 25 APOE ε4-) older adults in the Go, Stop, and NoGo conditions, respectively.

Behavioral Data Analyses

Age group effects. A series of t-tests were conducted to assess differences in accuracy and response latency between young and older adults. Accuracy variables included Percent Correct Target Trials (PCTT) in the Go condition and Percent Correct Inhibitory Trials (PCIT) in the Stop and NoGo conditions. Response latency variables included Reaction Time to Targets (RTT) in the Go condition and Stop Signal Reaction Time (SSRT) in the Stop condition.

With regard to accuracy, there were no significant difference in Go PCTT ($t(87) = -.88$, $p = .38$), Stop PCIT ($t(86) = -.93$, $p = .35$), or NoGo PCIT ($t(88) = -1.60$, $p = .11$) across groups. Significant differences in reaction times emerged, such that older adults exhibited significantly slower Go RTT ($t(87) = 8.54$, $p < .001$, $d = 1.82$) and Stop SSRT ($t(86) = 10.35$, $p < .001$, $d = 2.20$) than young adults (Figure 3).

Genetic risk group effects. Genetic risk group analyses were analogous to age group analyses, with a series of t-tests being conducted to assess differences in accuracy and response latency between APOE ε4+ and APOE ε4- groups.

Regarding accuracy, there were no significant differences in Go PCTT ($t(45)= -1.00$, $p = .32$), Stop PCIT ($t(44) = ..69$, $p = .50$), or NoGo PCIT ($t(46)= .55$, $p = .59$) across genetic risk groups. There were also no significant reaction time differences for Go RTT ($t(45) = -.74$, $p = .47$) or Stop SSRT ($t(44) = -.32$, $p = .75$).

Taken together, these results indicate significant differences in response latency, but not accuracy, across age groups and no accuracy or response latency differences across genetic risk groups. Descriptive statistics for these behavioral variables are presented in Table 2.

ERP Analyses

Age group effects. Six mixed 2x2x4 ANOVAs including the factors *Group* (Young/Old), *ERP Measure* (Amplitude/Latency) and *Electrode* (Fz, FCz, Cz, Pz) were conducted to assess N2 and P3 ERP differences across age groups for Go, Stop, and NoGo trials. The primary results of the interest were the overall 3-way *Group* x *ERP Measure* x *Electrode* interaction and corresponding pairwise comparisons, which were examined as appropriate based on the significance of this interaction (results presented in Table 3).

In the Go condition, a significant *Group* x *ERP Measure* x *Electrode* interaction ($F(3, 252) = 10.65$, $p < .001$) was seen for the N2 ERP in response to Go trials. Pairwise comparisons revealed significantly more negative N2 amplitudes at FCz and Cz and significantly longer N2 latencies at Fz and FCz for young adults compared to older adults. The 3-way interaction was also significant for the P3 ERP ($F(3, 252) = 7.42$, $p < .001$). Older adults exhibited significantly more positive amplitudes at Fz, while younger adults exhibited significantly more positive amplitudes at Cz and Pz. Older

adults exhibited significantly longer P3 latencies at Pz. Considered along with the average Go trial waveforms depicted in Figure 4, this pattern of results appears to reflect a somewhat attenuated neural response in older adults compared to young adults.

In the Stop condition, the *Group* x *ERP Measure* x *Electrode* interaction was significant for both N2 ($F(3, 258) = 8.33$, $p < .001$) and P3 ($F(3, 258) = 5.17$, $p < .001$) in response to Stop trials. For N2, older adults exhibited significantly more negative amplitudes and significantly longer latencies at FCz, Cz, and Pz. For P3, younger adults exhibited significantly more positive amplitudes at FCz, Cz, and Pz. Older adults exhibited longer P3 latencies at all electrodes (Fz, FCz, Cz, Pz). This pattern of results suggests an overall delayed neural responding in the older adult group, as evidence by longer peak latencies, which is consistent with behavioral findings of slower SSRTs in older adults. Variable differences in amplitude were seen, with older adults exhibiting greater N2 amplitudes and young adults exhibiting greater P3 amplitudes. Average Stop trial waveforms for each age group are presented in Figure 5.

In the NoGo condition, the *Group* x *ERP Measure* x *Electrode* interaction was significant for both N2 ($F(3, 258) = 2.76$, $p = .04$) and P3 ($F(3, 258) = 9.76$, $p < .001$) in response to NoGo trials. For N2, younger adults exhibited significant more negative amplitudes at Cz and Pz. There were no significant N2 latency differences. For P3, older adults exhibited more positive amplitudes at Fz, while more positive amplitudes were seen among younger adults at Cz and Pz. With regard to latency, older adults exhibited longer P3 latencies at Fz and Pz, while young adults exhibited longer P3 latencies at Cz. This pattern of results is generally consistent with an attenuated neural response (i.e., less

extreme peak amplitudes) in older adults compared to younger adults. Average NoGo trial waveforms for each age group are presented in Figure 6.

Genetic risk group effects. Following the same analysis framework as the age group analyses, six mixed 2x2x4 ANOVAs including the factors *Group* (APOE ε4+/ APOE ε4-), *ERP Measure* (Amplitude/Latency) and *Electrode* (Fz, FCz, Cz, Pz) were conducted to assess N2 and P3 ERP differences between genetic risk groups for Go, Stop, and NoGo trials. Again, the primary results of the interest were the overall 3-way *Group* x *ERP Measure* x *Electrode* interactions and, as relevant based on interaction significance, the corresponding pairwise comparisons (results presented in Table 3).

In the Go condition, the overall 3-way interaction was not significant for N2 ($F(3, 129) = 1.41$, $p = .24$) or P3 ($F(3, 129) = 2.01$, $p = .12$). As such, pairwise comparisons for these analyses were not examined.

In the Stop condition, a significant 3-way interaction was seen for N2 ($F(3, 132) = 4.87$, $p = .003$), but not P3 ($F(3, 132) = 1.34$, $p = .27$). Pairwise comparisons for the N2 ERP revealed significantly more negative N2 amplitudes in the APOE ε4+ group at Fz, FCz, and Cz and significant longer latencies in the APOE ε4+ group at Fz. This pattern of results is indicative of significantly more negative N2 amplitudes among APOE ε4+ elders, with a graded pattern of significance from anterior (highly significant) to posterior (non-significant) electrodes. Average Stop trial waveforms for each genetic risk group are presented in Figure 7.

In the NoGo condition the overall 3-way interaction was not significant for N2 ($F(3, 135) = .31$, $p = .94$) or P3 ($F(3, 135) = .42$, $p = .74$). As such, pairwise comparisons for these analyses were not examined.

Relationships Between Behavioral Data and ERP Variables

In order to more fully understand the relationship between behavioral task performance and underlying neural processing, a variety of exploratory correlation analyses were conducted. These analyses focused specifically on behavioral variables related to inhibitory control, namely Stop PCIT, Stop SSRT, and NoGo PCIT. Given the role of frontal brain networks in modulating inhibitory control, these analyses focused specifically on two frontal electrodes, namely Fz and FCz. Correlation analyses were conducted separately for the Stop and NoGo conditions. Correlations among the entire sample were examined first, followed by correlations separated by age and genetic risk groups.

For the Stop condition, correlations were conducted for the Stop PCIT and Stop SSRT behavioral variables and the ERP variables for N2 and P3 amplitude and latency at Fz and FCz. Within the full sample, a significant negative correlation was seen between Stop PCIT and Stop SSRT, indicating that longer reaction times to stop signals were associated with poor inhibitory performance on Stop trials. No significant correlations were seen between Stop PCIT and any of the ERP variables. However, significant negative correlations were seen between SSRT and N2 and P3 amplitudes at FCz. Although both of these correlations are negative, the interpretation of this association varies for N2 and P3 since N2 amplitudes are in the negative range and P3 amplitudes are in the positive range. Specifically, these correlations indicate that longer reaction times to stop signal are associated with greater N2 peak amplitudes, but smaller P3 peak amplitudes (Figure 8). Additionally, longer SSRTs were associated with longer N2 latencies at FCz and longer P3 latencies at Fz and FCz.

Follow-up analyses were conducted to determine whether this pattern of Stop condition correlations differed by age group or genetic risk group. Interesting, while the negative correlation between Stop SSRT and Stop PCIT remained significant in young adults and older adults and in the APOE ε4+ group, the vast majority of the correlations with ERP variables were no longer significant in any of the age or genetic risk groups. Results of these Stop condition correlation analyses for the entire sample as well as broken down by group are presented in Table 4. These results indicate that SSRT is associated with ERP variables when examining participants across the lifespan, but not when examining subgroups that have more homogenous age distributions.

For the NoGo condition, correlations were conducted for the NoGo PCIT behavioral variable and the ERP variables for N2 and P3 amplitude and latency at Fz and FCz. Within the overall sample, NoGo PCIT was not significantly correlated with any of the ERP variables.

Follow-up analyses were conducted for these same variables within the different age and genetic risk groups. Within the young adults, NoGo PCIT was significant correlated with P3 amplitude at Fz, such that better performance was associated with greater amplitude. No significant correlations between NoGo PCIT and ERP variables were seen in the older adult group. However, when the older adult group was broken down by APOE ε4 risk, significant correlations did emerge. Within the APOE ε4+ group, results indicated significant negative correlations between NoGo PCIT and P3 amplitude at both Fz and FCz, indicating that better NoGo performance was associated with smaller P3 amplitudes. However, within the APOE ε4- group, results indicated significant negative correlations between NoGo PCIT and N2 latency at Fz and FCz,

indicating that better NoGo performance was associated with shorter N2 latencies. Results of these NoGo condition correlation analyses for the entire sample as well as broken down by group are presented in Table 5.

Discussion

This study is the first to examine the relationship between genetic risk for AD (by APOE ε4 inheritance), inhibitory control, and neural activity measured by ERPs. We explored differences in behavioral task performance and neural activity during an inhibitory control task as a function of age (young and older adults) and genetic risk for AD (APOE ε4+/-) in order to elucidate changes in executive functioning across the lifespan and potential markers of risk for developing AD.

Behaviorally, response accuracy across age groups did not significantly differ for target trials in the Go condition or for inhibitory trials in the Stop and NoGo conditions. These latter findings in the inhibitory task conditions were contrary to our prediction that inhibitory deficits in older adults would drive group differences on Stop and NoGo trials. Although this result was not anticipated, it is fitting with the results of Wetter et al. (2005) who found genetic risk group differences on an Inhibition/Switching but not the Inhibition Only condition of the DKEFS CWIT. It is difficult to determine whether our prediction of PGNGS difficulty falling between these two CWIT conditions is accurate; however, it seems that a task more cognitively demanding than the PGNGS may be needed to detect age group differences when examining an older adult sample that is comprised entirely of cognitively intact elders. Despite this lack of difference in target and inhibitory accuracy, hypothesized differences in reaction time did emerge, such that

older adults exhibited significantly slower reaction times than young adults across all task conditions (Go, Stop, and NoGo).

Regarding the effects of genetic risk on behavioral task performance, no significant differences in response accuracy or reaction times emerged between those who carry the APOE ε4 allele and those who do not. Although this was also contrary to our prediction that the APOE ε4+ group would show poorer inhibitory performance, these results speak to the inherent issue with using neuropsychological testing to assess group differences in healthy *at-risk* groups. Specifically, these findings, in conjunction with the lack of accuracy differences between age groups, highlight the cognitively intact nature of our sample and the limited ability of neuropsychological testing to detect subtle differences in healthy elders who may be at risk of developing dementia but are not yet showing signs of cognitive decline.

In addition to behavioral measures, this study examined peak amplitude and latency for two ERPs of interest, N2 and P3, which are commonly examined in the context of executive functioning tasks and generally purported to reflect inhibitory processing (Enriquez-Geppert et al., 2010; Falkenstein et al., 2002; Polich, 2007). The N2 ERP has been shown to reflect inhibitory control and conflict monitoring (Falkenstein et al., 2002; van Boxtel et al., 2001), (however, see also Donkers & van Boxtel, 2004; Smith, Johnstone, & Barry, 2007), while the P3 ERP may reflect more attentional processing and allocation in the context of inhibitory demands (Polich, 2007; Polich & Kok, 1995). One study described the N2 ERP as reflective of the "active inhibitory processes that determine the success of an attempted withhold of motor action" and described P3 as reflective of performance evaluation and error detection (Roche et al.,

2005, p. 68). For the present study, we were particularly interested in assessing these ERPs to determine the degree to which the neural activity that subserves executive functioning may be a more sensitive marker of aging and risk for AD than behavioral measures based on neuropsychological testing.

A variety of age-related differences in N2 and P3 amplitude and latency emerged, some of which were in the predicted direction and others of which were not. Consistent with our hypotheses, older adults tended to exhibit longer ERP latencies (for N2 and P3) than young adults. Significant N2 and P3 amplitude differences between the young adult and older adult groups emerged in all three task conditions and at the majority of the electrode sites assessed. However, the direction of these differences varied somewhat as older adults exhibited greater amplitudes in some instances (N2: FCz, Cz, and Pz in the Stop condition; P3: Fz in the Go and NoGo conditions) and young adults exhibited greater amplitudes in others (N2: FCz and Cz in the Go condition, Cz and Pz in the NoGo condition; P3: FCz, Cz, and Pz in the Stop condition, Cz and Pz in the Go and NoGo conditions). Although there is not a clear pattern of one group exhibiting consistently greater amplitudes than the other, latencies findings are generally consistent with the behavioral findings of slower reaction times and the overall interpretation of slowing cognitive abilities with increased age.

Differences that emerged between the genetic risk groups were particularly notable and important with regard to markers of AD risk. We found significant amplitude differences for the N2, but not P3, ERP, such that those who carry the APOE ε4 allele exhibited significantly more negative N2 amplitudes during the Stop condition than those who do not. These differences were robust at frontal and central electrodes. Moreover, a

graded pattern of significance and effect size emerged, such that the magnitude of difference was largest at electrodes over frontal regions and decreased through more posterior electrodes. Interestingly, these differences were not in the expected direction given that older adults were predicted to have *smaller* ERP amplitudes for inhibitory trials due to inefficient inhibitory functioning. However, the pattern of results may be explained by processes related to compensatory neural functioning, which are explained in greater details below. Also importantly, while robust differences were seen in both the behavioral data and the ERPs in age group analyses, ERP differences across genetic risk groups emerged in the *absence* of any differences in behavioral performance. This pattern of results highlights ERPs as potentially more sensitive markers of AD risk than neuropsychological testing. Such ERP markers are critical to explore as AD research focuses increasing on early detection of diseases processes and specifically targets individuals who *lack* detectable cognitive deficits. In many ways, research should expect to see a paucity of behavioral task differences among these early stage or at-risk populations given that any significant differences on neuropsychological testing may represent cognitive deficits that signal progression to a later stage of disease progression.

Compensatory theories of cognitive aging appear to fit with a variety of the findings from this study. Such theories describe the mechanisms underlying structural and physiological changes that occur in the brain throughout the aging process that are compensated for by reorganization of brain functioning (Cabeza, 2002). In older adults this can manifest as greater or lesser activity in certain brain regions compared to younger adults, representing a combination of less efficient processing and compensatory functioning through recruitment of additional brain regions (Cabeza et al., 1997). The

scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2010) posits that compensatory scaffolding, which occurs through recruitment of additional neural circuitry, helps to offset the cost of declining functioning in brain regions that have become inefficient. According to STAC, increased recruitment of frontal regions in particular helps to maintain performance in older adults.

Variations in the pattern of overactivation and underactivation can also be a function of differences in task difficulty. For example, older adults often recruit additional brain regions and show more overactivation on tasks of lower cognitive demand in order to match the performance of young adults, who recruit more specialized, focal regions (Reuter-Lorenz & Park, 2010). However, as tasks demands increase, young adults also shift to a more overactive pattern of neural recruitment in order to maintain performance, while older adults are unable to maintain this increase (having already maxed out at the lower cognitive load) and exhibit underactivation relative to young adults and decreases in performance (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2010).

Results of the present study are consistent with this compensatory processing model in a number of ways. In the Stop condition, N2 ERP differences followed a pattern of greater peak amplitude in older adults across numerous electrodes sites, specifically FCz, Cz, and Pz, though no such difference were seen in the NoGo condition. These findings may be due to relative differences in the difficulty of these task conditions and the impact of this difficulty on compensatory functioning. Results of behavioral analyses revealed that task accuracy was poorest in the Stop condition for all groups. To further assess the role of task difficulty in possible compensatory functioning, follow-up analyses

within the young and older adults groups were conducted to examine accuracy difference across conditions (rather than across groups). Results indicated that inhibitory accuracy was significantly worse in the Stop condition than the NoGo condition for younger adults, but that task accuracy across these conditions did not differ significantly for older adults. This was due to older adults performing relatively poorly in both the Stop and NoGo conditions, while younger adults only exhibited this drop in accuracy in the more difficult Stop condition. In order to adapt to this greater level of difficulty in the Stop condition, older adults appear to have exhibited increased neural activity (manifest as greater N2 amplitudes) so as to maintain a comparable level of performance as young adults and avoid taking a further hit to their task accuracy.

Differences across genetic risk groups also follow this compensatory functioning model. Greater N2 amplitudes among those with the APOE ε4 allele, compared to non-carriers, likely reflect compensatory activation in these individuals. The pattern of greatest significant differences and effect sizes at frontal electrodes, with decreasing significance throughout more posterior electrodes (to non-significance at Pz), also seems fitting with the tendency for greater recruitment of frontal regions based on the STAC model, though it is difficult to discern the degree to which this may have been more so due simply to the executive nature of the task.

Another critically important aspect of this study is the support it lends for the utility of Stop Signal tasks as a specific executive functioning marker of risk for AD and cognitive change with age. Significant ERP differences by genetic risk were seen solely for N2 in the Stop condition and older adults showed significantly greater N2 amplitudes in the Stop condition. Based on these findings, this specific condition of the PGNGS task

appears to tap into the neural differences that underlie task performance, for which behavioral group differences are not yet apparent. Additionally, the Stop Signal Reaction Time (SSRT) metric, which is unique to the Stop condition and allows for a quantification of inhibitory trial performance that is not possible in the NoGo condition, was significantly correlated with a number of ERP variables (both amplitude and latency) in the overall sample. Interestingly, these significant associations were not seen among separate age and genetic risk groups, suggesting that Stop Signal Reaction Time and underlying neural activity are related across the lifespan, but that changes in these metrics may occur gradually since they were not significantly correlated among the more homogenous subgroups.

Beyond the specific aspects of the PGNGS task that provide novel markers of risk for AD, another highly valuable aspect of the present study is that these significant findings were seen specifically in the context of an inhibitory control task, underscoring the importance of examining executive functioning abilities as preclinical markers of AD. Executive deficits are common in AD and among the first non-memory deficits to emerge (Amieva, Phillips, Della Sala, & Henry, 2004). Given the high rate of executive deficits in AD patients and the role of executive abilities in tasks such as ADLs, this domain of cognitive functioning is an important area for further research as we work toward elucidating cognitive and neural markers of AD risk and disease progression.

While executive abilities represent a standalone domain of interest, they also warrant critical consideration with regard to the role that executive functioning plays in memory demands. Memory decline is indeed a central factor in the development and progression of AD and a defining characteristic of AD pathology (American Psychiatric

Association, 2013); however, declines in executive abilities have been suggested to mediate declines in cognitive domains including memory (Balota, Dolan, & Duchek, 2000; Gleichgerrcht, Torralva, Martinez, Roca, & Manes, 2011; Goh & Park, 2009). For example, increased frequency of intrusion errors, commonly thought to represent executive deficits such as impairment in self-monitoring and error detection, has been identified as one of five specific characteristics of episodic memory that differentiate individuals with mild AD from cognitively intact older adults (Salmon & Bondi, 2009). Additionally, a recent study showed that AD patients with impaired, compared to those with intact, executive abilities performed more poorly on measures of story and wordlist memory and that recognition memory on these measures was significantly correlated with performance on measures of executive functioning (Gleichgerrcht et al., 2011). To this end, the present study provides evidence of a novel executive functioning marker of risk for AD, specifically N2 amplitude in the Stop Signal task, and provides a foundation for further research evaluating the role of inhibition as a predictor of memory deficits and overall cognitive decline.

Limitations and Directions for Future Research

Despite the many exciting advances that are supported by the present study, this work is not without limitations and certainly highlights many directions for future research.

The present sample is relatively small with less than 50 participants in each age group and only approximately 25 participants in each genetic risk group. Though the overall sample of 91 participants is fairly large for an ERP study, a greater sample size would be beneficial for increasing number of participants in each subgroup. Additionally,

a greater sample size would allow for further subdivision of the APOE ε4+ group in order to assess difference between homozygotes and heterozygote ε4 carriers. This would be beneficial for assessing further degrees of risk for AD as individuals with two ε4 alleles are more likely to develop AD than those with only one ε4 allele (Twamley et al., 2006).

Within the present sample genetic testing was conducted only for the older adult participants. Research regarding risk for AD by APOE ε4 inheritance is increasingly focusing on younger samples in the hopes of detecting who may be most likely to develop AD as early as possible (Filippini et al., 2011; Filippini et al., 2009; Reiman et al., 2004). We are aware of no such work that has focused on executive functioning specifically. Thus, extending the present research to an examination of young adults with varying degrees of risk based on APOE ε4 inheritance would be very beneficial. This type of research would provide further insight into whether the cognitive deficits and/or compensatory neural activity, seen in APOE ε4+ elders are comparable in young adults who possess the APOE ε4 allele, particularly in the context of executive functioning. This is an area demanding greater focus as some research as shown a differential effect of APOE ε4 across the lifespan, with APOE ε4 carriers actually showing better task performance when they are younger followed by over-recruitment of brain areas to compensate for declining cognitive function with increased age (Han & Bondi, 2008).

Finally, though ERP methodology offers high temporal resolution, its limited spatial resolution restricts the degree to which the functioning of specific brain structures or regions can be tied to the observed differences at particular electrodes. Advanced source localization techniques provide some opportunity for exploring this more thoroughly and have in fact been valuable in linking the N2 ERP in NoGo tasks to

functioning in medial frontal regions such as the anterior cingulate cortex (Bekker, Kenemans, & Verbaten, 2005). However, further work utilizing such techniques is necessary for better contextualizing ERP findings within a functional neuroanatomy framework.

Regarding additional directions for future research, a primary area of focus for extending this work should be the examination of other executive functioning measures to determine whether specific executive abilities are most associated with risk for AD. Other recent studies have shown differences in executive functioning performance across groups with varying risk for AD on measures such as the Wisconsin Card Sorting Test (Hazlett et al., 2015) and the DKEFS Color-Word Interference Test (Wetter et al., 2005). Taken together with the current findings, executive abilities including inhibition and set shifting appear to show particular promise as potential markers of risk for AD.

Further exploration of how specific executive abilities may impact memory functioning and relate to ADLs would also be greatly beneficial for better understanding the role of executive deficits in AD specifically. However, this line of research also begs the question of whether or not these findings are specific to AD or applicable to other types of dementia as well. For example, vascular dementia or frontotemporal dementia (FTD) are commonly characterized by various types of executive deficits and also carry the diagnostic criteria of impairment in the ability to complete ADLs (American Psychiatric Association, 2013). Prior research in these area suggests that patients with AD and vascular dementia exhibit poorer working memory and executive functioning than healthy controls, but that these dementia groups do not differ from each other on these measures (McGuinness, Barrett, Craig, Lawson, & Passmore, 2010). Research

comparing individuals with AD and FTD has shown that quantitative measures of executive functioning are similar across groups, while qualitative assessment of these results suggest that deficits in working memory are predominant in AD, while deficits in attention, set shifting and response inhibition are predominant in FTD (Stopford, Thompson, Neary, Richardson, & Snowden, 2012). Exploration of the relationships between executive abilities, ADLs, and additional risk factors for these dementias (e.g., cardiovascular risk factors) is needed to clarify how/if executive functioning is implicated as a marker of risk in these disorders as well and how the clinical evaluation of executive functioning may add value in predicting the onset of a dementing condition and identifying the specific etiology.

Conclusion

In conclusion, the present study revealed significant differences in the N2 ERP, which serves as an index of neural activity during inhibitory functioning, across genetic risk groups in a sample of cognitive intact older adults. These differences in neural activity were seen in the absence of differences in behavioral task performance across genetic risk groups, suggesting that electrophysiological measures may be more sensitive than neuropsychological testing to early changes associated with of risk for AD. These findings highlight the importance of considering N2 amplitudes in Stop Signal tasks as a novel, early marker of risk for AD. Moreover, the results of this study underscore the importance of considering cognitive domains beyond memory when exploring risk factors for AD and the value of examining executive abilities, such as inhibition specifically, as preclinical markers of risk for cognitive decline and dementia.

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Table 1

Sample Demographics (mean (± SD))

	Older Adults (n = 48)			Young Adults (n = 42)
	All Older Adults	APOE ε4+ (n = 23)	APOE ε4- (n = 25)	
Age (years)	79.02 (4.61)	78.30 (4.39)	79.68 (4.78)	19.86 (2.66)
Education (years)	14.77 (2.29)	15.65 (2.44) [a]	13.96 (1.84) [a]	14.05 (1.75)
Sex (% female)	72.9%	78.3%	68.0%	73.8%
DRS-2	138.13 (3.03)	137.04 (3.02)	138.88 (2.89)	-

Note. APOE = Apolipoprotein-E; DRS-2 = Dementia Rating Scale-Second Edition.
[a] Significant genetic risk group differences at the $p < .01$ level.

Table 2

Descriptive Statistics for Behavioral Variables (mean (± SD))

	Older Adults			Young Adults
	All Older Adults	APOE ε4+	APOE ε4-	
Accuracy				
Go PCTT	99.54 (.82)	99.55 (.92)	99.52 (.74)	99.51 (1.50)
Stop PCIT	75.00 (11.92)	73.68 (14.58)	76.11 (9.28)	77.45 [b] (12.70)
NoGo PCIT	77.72 (15.35)	76.45 (15.51)	78.89 (15.42)	82.67 [b] (13.81)
Reaction Time				
Go RTT (ms)	676.01 [a] (48.49)	681.35 (50.68)	670.89 (46.80)	595.55 [a] (39.29)
Stop SSRT (ms)	541.47 [a] (36.89)	543.38 (34.61)	539.87 (39.34)	451.38 [a] (44.69)

Note. APOE = Apolipoprotein-E; PCTT = Percent Correct Target Trials; PCIT = Percent Correct Inhibitory Trials; RTT = Reaction Time to Targets; SSRT = Stop Signal Reaction Time.

[a] Significant age group differences at the $p < .001$ level

[b] Significant differences between task conditions at the $p < .001$ level

Table 3

Results of Pairwise Comparisons for Analyses with Significant Group x *ERP Measure* x *Electrode Interactions*

Trial Type	Electrode	N2						P3					
		Amplitude			Latency			Amplitude			Latency		
		F	*d*		*F*	*d*		*F*	*D*		*F*	*d*	
Age Group Effects													
Go	Fz	.21	-	-	24.14***	-1.04	Y > O	14.52***	.82	O > Y	.68	-	-
	FCz	5.90*	.52	Y > O	10.70***	-.70	Y > O	.23	-	-	.00	-	-
	Cz	5.67*	.52	Y > O	1.37	-	-	22.38***	-1.01	Y > O	.00	-	-
	PZ	.39	-	-	3.20	-	-	30.09***	-1.18	Y > O	59.41***	1.68	O > Y
Stop	Fz	.04	-	-	1.82	-	-	1.91	-	-	5.69*	.50	O > Y
	FCz	4.99*	-.48	O > Y	34.01***	1.24	O > Y	6.16*	-.52	Y > O	24.81***	1.46	O > Y
	Cz	17.79***	-.90	O > Y	80.80***	1.91	O > Y	31.27***	-1.18	Y > O	60.63***	1.68	O > Y
	PZ	13.45**	-.78	O > Y	28.48***	1.15	O > Y	30.01***	-1.16	Y > O	6.33*	.54	O > Y
NoGo	Fz	2.35	-	-	.69	-	-	10.70**	.70	O > Y	9.09**	.65	O > Y
	FCz	.79	-	-	.86	-	-	1.45	-	-	.23	-	-
	Cz	7.48**	.58	Y > O	.36	-	-	8.47**	-.61	Y > O	9.80**	-.68	Y > O
	PZ	7.11**	.57	Y > O	3.74	-	-	33.31***	-1.22	Y > O	5.57*	.51	Y > O
Genetic Risk Group Effects													
Stop	Fz	19.06***	1.31	ε4+>ε4-	5.78*	-.73	ε4+>ε4-						
	FCz	10.94**	1.00	ε4+>ε4-	1.08	-	-						
	Cz	6.89*	.78	ε4+>ε4-	.90	-	-						
	PZ	1.33	-	-	1.84	-	-						

Note. ε4 = Apolipoprotein-E ε4. *$p < .05$, ** $p < .01$, *** $p < .001$.

Table 4

Correlations between Stop SSRT and Behavioral and ERP Variables In the Stop Condition Within the Full Sample and Age and Genetic Risk Groups

	Stop PCIT	Stop Trial N2				Stop Trial P3			
		Fz Amplitude	FCz Amplitude	Fz Latency	FCz Latency	Fz Amplitude	FCz Amplitude	Fz Latency	FCz Latency
Full Sample	-.34**	-0.08	-.23*	.90	.48***	0.08	-.31**	.36**	.51***
Young Adults	-.48**	-.13	-.05	-.01	.21	-.02	-.22	.34*	.29
Older Adults	-.33*	-.17	-.14	-.04	.08	-.11	-.10	.14	.22
APOE ε4+	-.50*	.21	.23	-.11	.04	.03	.01	.30	.29
APOE ε4-	-.14	-.40	-.31	-.05	.10	-.20	-.16	.05	.20

Note. APOE = Apolipoprotein-E; SSRT = Stop Signal Reaction Time; PCIT = Percent Correct Inhibitory Trials.
*$p < .05$, ** $p < .01$, *** $p < .001$.

Table 5

Correlations between NoGo PCIT and ERP Variables in the NoGo Condition Within the Full Sample and Age and Genetic Risk Groups

	Stop Trial N2				Stop Trial P3			
	Fz Amplitude	FCz Amplitude	Fz Latency	FCz Latency	Fz Amplitude	FCz Amplitude	Fz Latency	FCz Latency
Full Sample	.15	.06	-.14	.03	.01	-.09	.03	-.11
Young Adults	.10	.02	-.17	.13	.33*	.00	.21	-.13
Older Adults	.15	.12	-.15	-.12	-.16	-.14	.00	-.08
APOE ε4+	.10	-.08	.20	.24	-.53*	-.49*	.03	-.08
APOE ε4-	.19	.23	-.56**	-.47*	.08	.10	-.03	-.05

Note. APOE = Apolipoprotein-E; PCIT = Percent Correct Inhibitory Trials.
*$p < .05$, ** $p < .01$, *** $p < .001$.

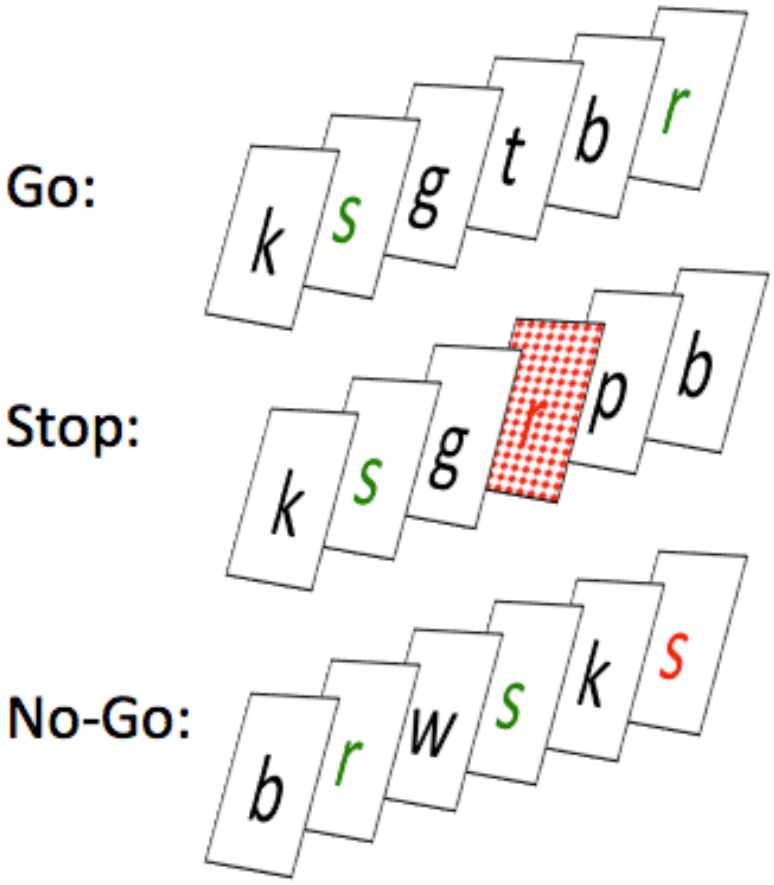


Figure 1. The 3 conditions of the PGNGS task. In the Go condition, participants respond to all "r"s and "s"s. In the Stop condition, participants respond to "r"s and "s"s, unless they are interrupted by a red flash (depicted by red checkerboard above). In the NoGo condition, participants respond to "r"s and "s"s in alternation (i.e., never respond to the same letter twice in a row).

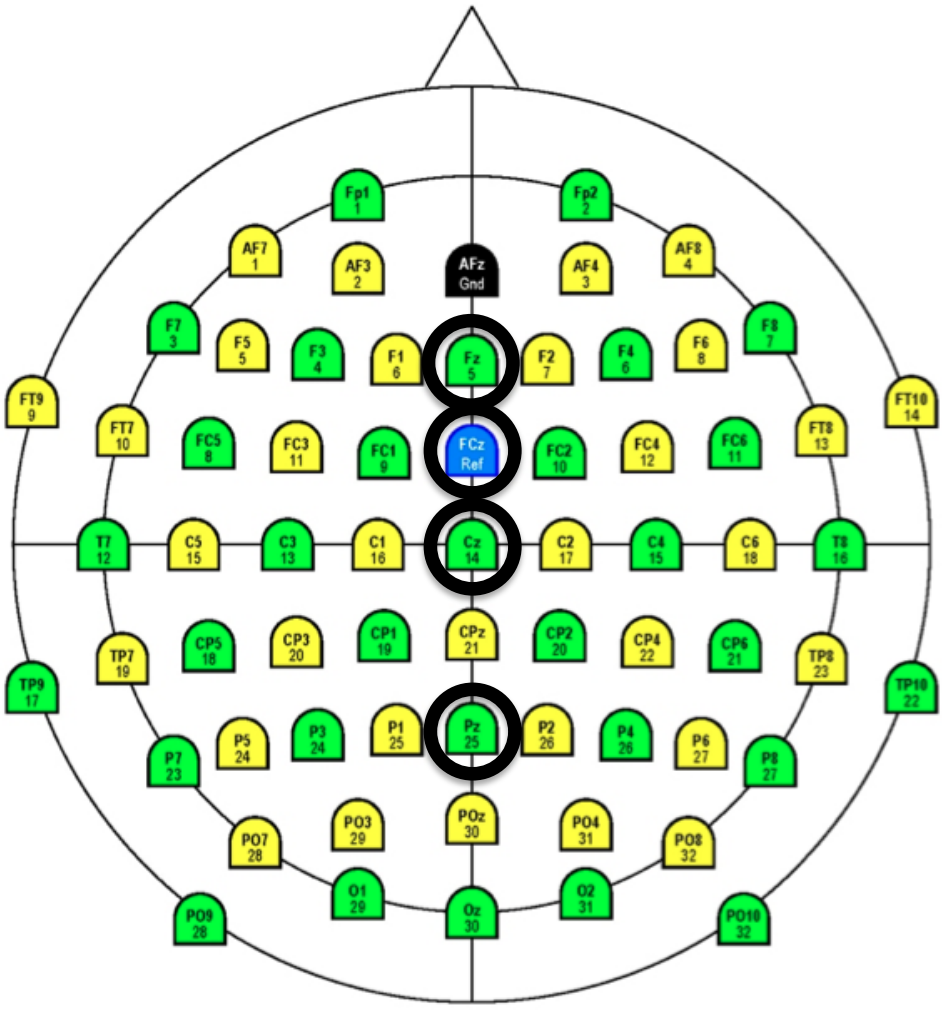


Figure 2. Arrangement of electrodes on Brain Products 64-active electrode cap (actiCAP, Brain Products, Gilching, Germany, www.brainproducts.com). Electrodes of interest in the present study are indicated by black circles.

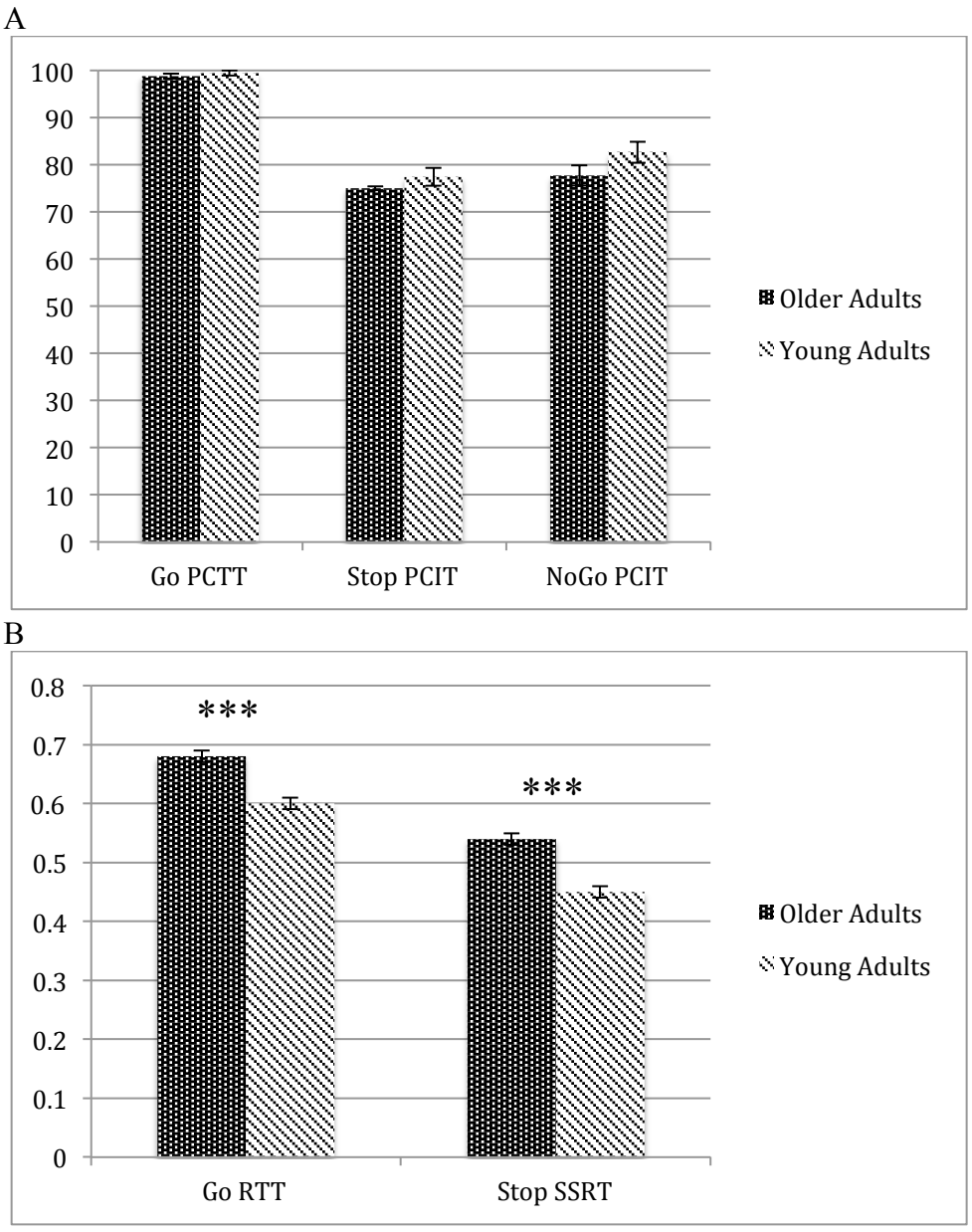


Figure 3. Age differences in behavioral task performance. There were no significant differences in task accuracy by age (Panel A). Older adults exhibited significantly slower reaction times than young adults across to Go and Stop trials (Panel B). (Error bars represent standard errors.)
*** $p < .001$.

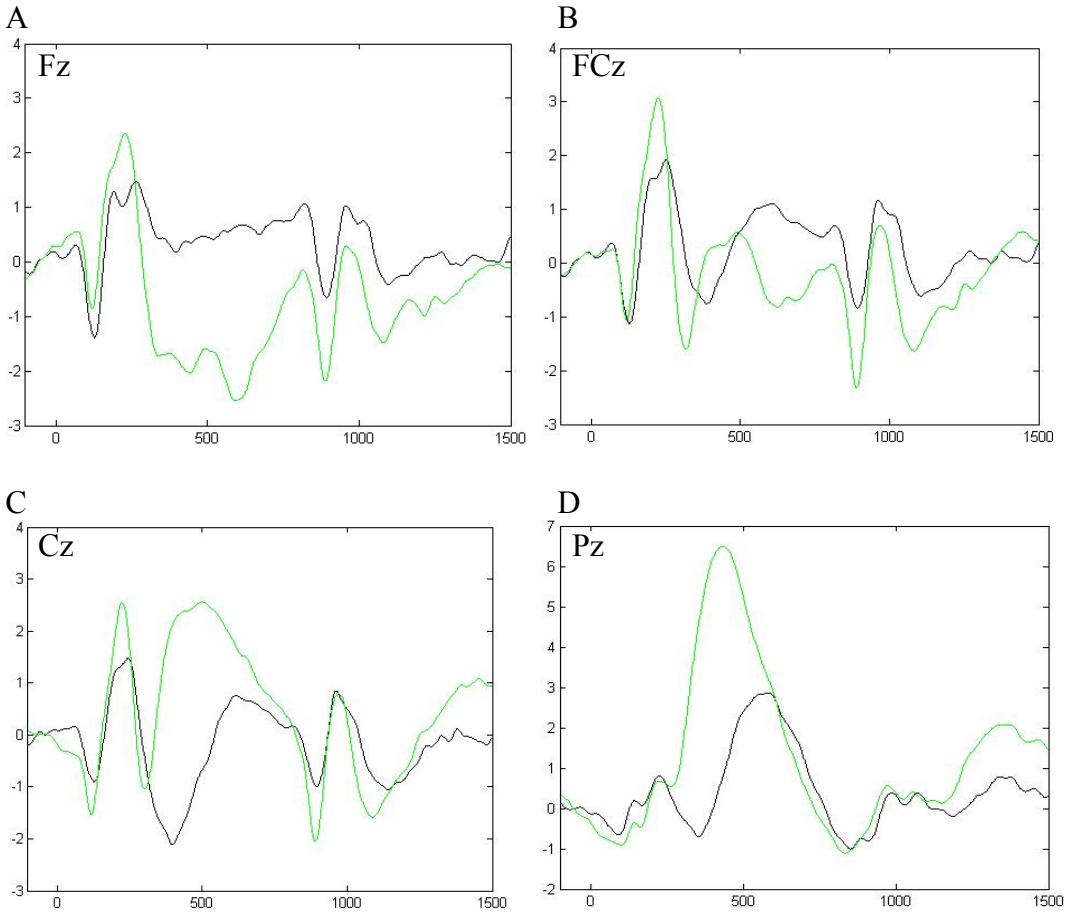


Figure 4. Age differences in ERPs elicited by Go trials at Fz (Panel A), FCz (Panel B), Cz (Panel C), and Pz (Panel D). (Black = Older Adults; Green = Young Adults)

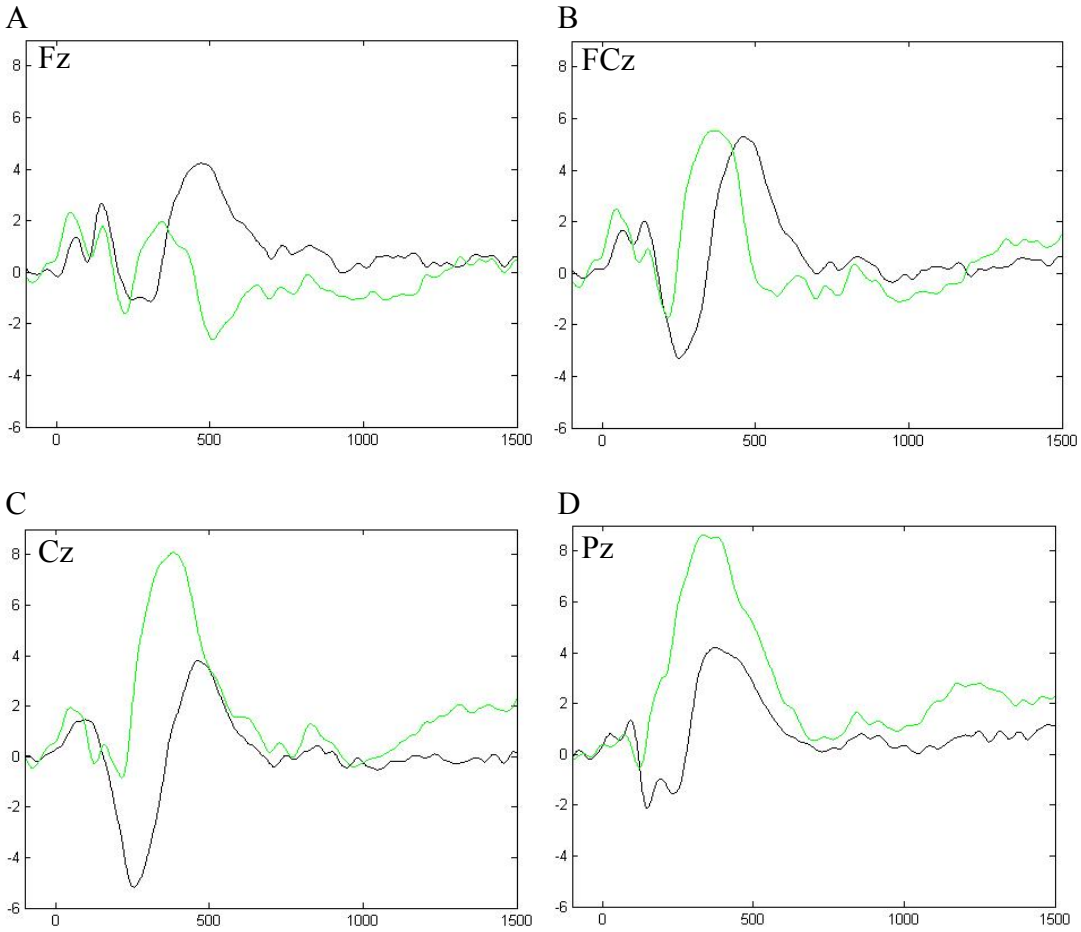


Figure 5. Age differences in ERPs elicited by Stop trials at Fz (Panel A), FCz (Panel B), Cz (Panel C), and Pz (Panel D). (Black = Older Adults; Green = Young Adults)

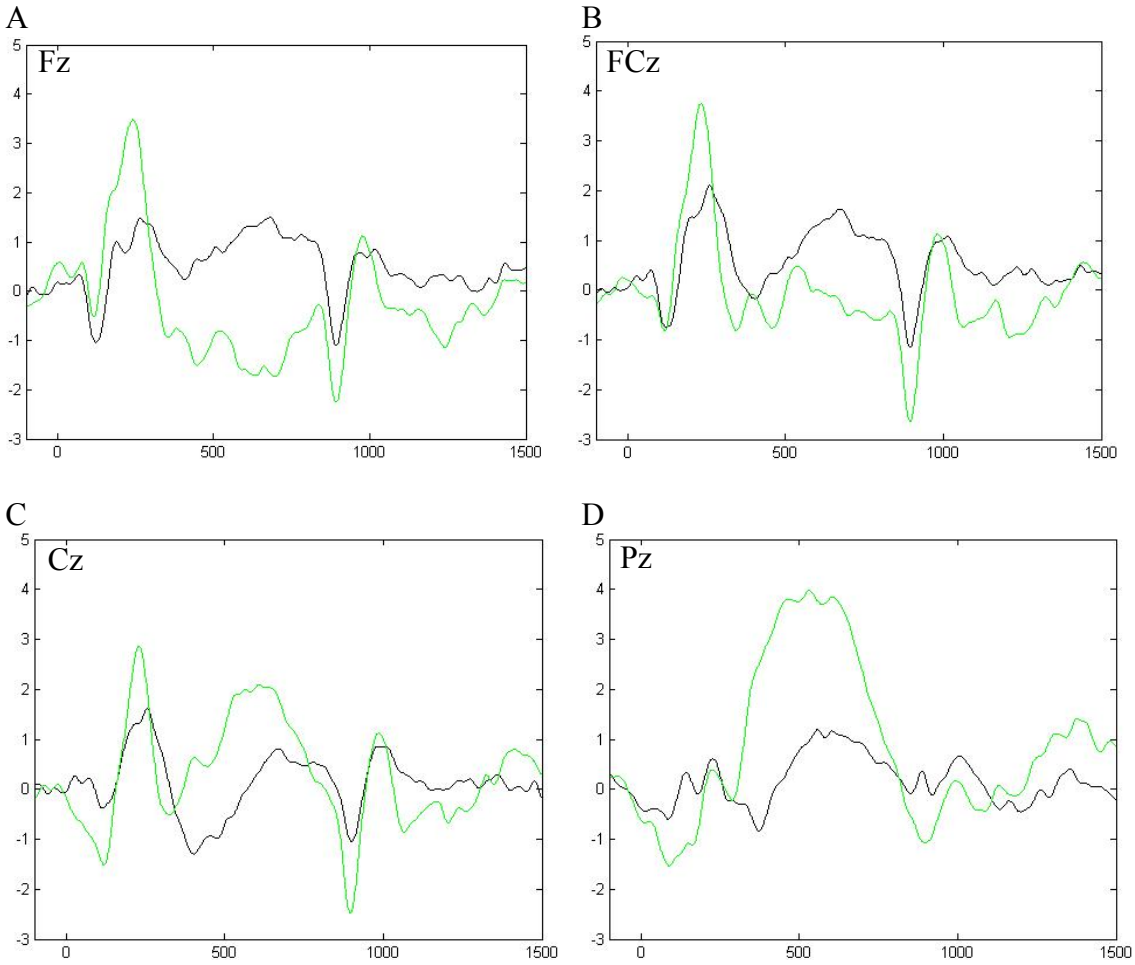


Figure 6. Age differences in ERPs elicited by NoGo trials at Fz (Panel A), FCz (Panel B), Cz (Panel C), and Pz (Panel D). (Black = Older Adults; Green = Young Adults)

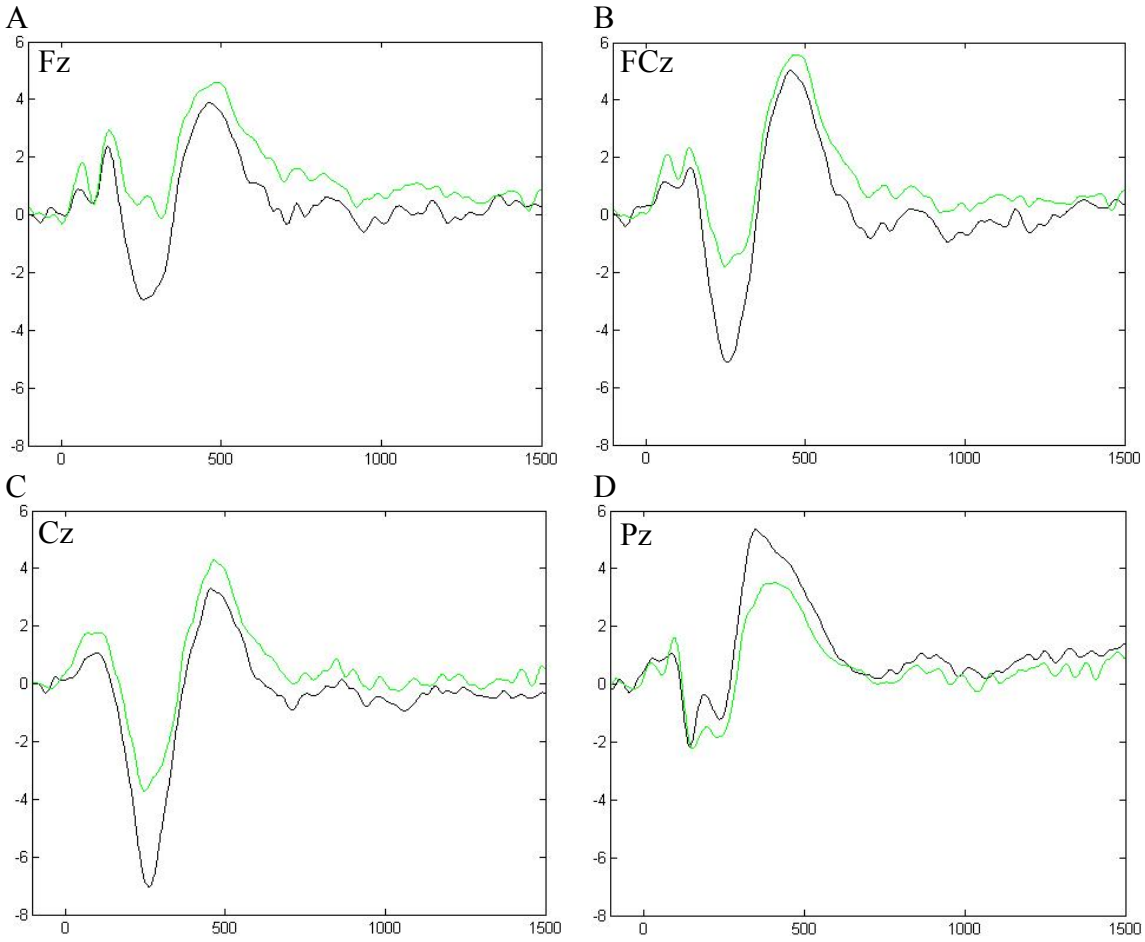
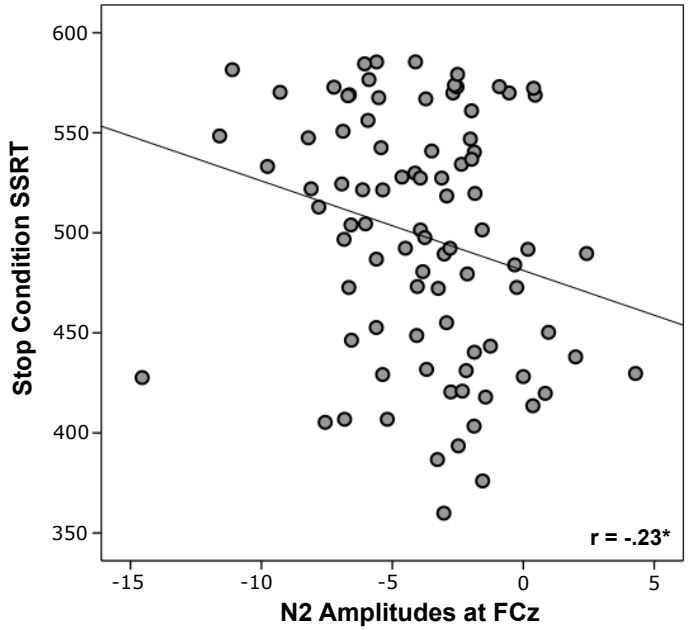


Figure 7. Genetic risk differences in ERPs elicited by NoGo trials at Fz (Panel A), FCz (Panel B), Cz (Panel C), and Pz (Panel D). (Black = APOE ε4+; Green = APOE ε4-)

A



B

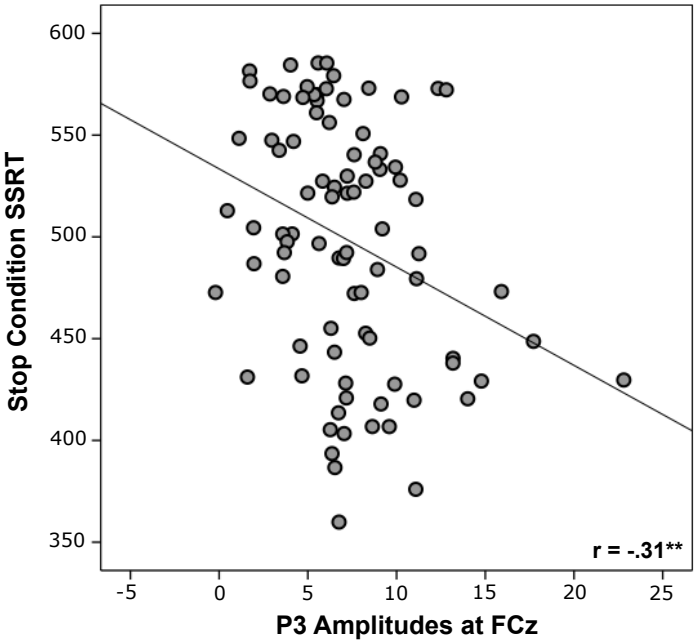


Figure 8. Scatterplots depicting the correlations between Stop SSRT and N2 (Panel A) and P3 (Panel B) amplitudes at FCz during the Stop condition.
*$p < .05$, ** $p < .01$.