Response Inhibition-Related Beta Power: Distinguishing Cognitively Intact Elders by Risk for Alzheimer's Disease

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RESPONSE INHIBITION-RELATED BETA POWER: DISTINGUISHING COGNITIVELY INTACT ELDERS BY RISK FOR ALZHEIMER'S DISEASE

by

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ABSTRACT
RESPONSE INHIBITION-RELATED BETA POWER: DISTINGUISHING COGNITIVELY INTACT ELDERS BY RISK FOR ALZHEIMER'S DISEASE

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Current neuropsychological research demonstrates an association between the Apolipoprotein-E ε4 allele (APOE ε4) and poorer cognitive outcomes in older adults. However, there is a general lack of consensus regarding the effect the ε4 allele has on executive functioning in cognitively intact older adults, and there is even less study of the effects the ε4 allele has on specific executive function processes, such as response inhibition. While behavioral task performance may lack the sensitivity to detect subtle differences in cognitively intact, at-risk individuals, neural activity may better differentiate between individuals who are more likely to develop Alzheimer's disease (AD). Compensatory theories of aging posit at-risk individuals may employ compensatory mechanisms in the form of bilateral neural recruitment and greater frontal activation. While electrophysiological methods, such as ERP and EEG, have been employed to investigate neural activity related to the ε4 allele, few studies have examined the differences in these neural markers between cognitively intact older adult carriers and non-carriers. The present study examined EEG oscillatory activity as a biomarker to target these gaps in the existing literature by investigating event-related beta activity in cognitively intact ε4 carriers (n = 21) and non-carriers (n = 23) during a response inhibition task. Our findings support compensatory theories of aging by demonstrating cognitively intact older adults employ compensatory mechanisms in the form of bilateral recruitment and greater frontal recruitment specifically during a task requiring inhibitory control. Additionally, these compensatory mechanisms are even greater in individuals at greater risk for developing AD. Results underscore the utility of assessing task-related neural activation during executive function tasks so as to better differentiate individuals at an increased risk for future cognitive impairment. The present study further demonstrates that EEG oscillatory activity, and more specifically beta band activity, may be a useful prodromal marker of cognitive decline.

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As of 2018, roughly 5.7 million Americans were estimated to be living with Alzheimer's disease (AD), a number that is expected to dramatically increase as the baby boomer generation continues to age (Alzheimer's Association, 2018). Most traditionally, memory decline is thought to be the initial indicator of AD, as poor memory is the primary hallmark of the disease. Recently, however, other important cognitive domains have been implicated in early AD-related changes. With a growing aging population, early identification and prevention is critical for disease modification, as well as for lowering the economic impact of AD (Barnett et al., 2014). As such, better characterization of non-amnestic prodromal markers of AD may facilitate early disease identification and prevention.

Executive Function During Aging

Despite the hallmark status of memory impairment in AD, executive function is a cognitive domain that has gained increased attention within the literature. Executive function is considered an umbrella term that involves multiple cognitive processes that work in concert to accomplish goal-directed behaviors (Elliott, 2003). Core cognitive processes encompassed by the broader executive function umbrella include continuous monitoring of working memory (updating), switching between tasks (shifting), and countermanding dominant or prepotent responses (inhibition; Miyake et al., 2000; Smith & Jonides, 1999). These processes, predominantly mediated by the prefrontal cortex, play an important role in successful completion of day-to-day activities. As such, age-

associated reductions in frontal and parietal volume may underlie executive function decline demonstrated during the aging process (Fjell et al., 2016; Rae et al., 2015; Resnick et al., 2003) and may impact future functional impairment (Marshall et al., 2011).

Executive Function in mild cognitive impairment and AD

Deficits in executive function beyond what have been identified in normal aging are observed within an AD and mild cognitive impairment (MCI) population. Individuals with AD demonstrate deficits in the ability to manipulate working memory, shift attentional resources, and in inhibitory control (Collette et al., 1999). Specifically, impairment in these processes has been linked to dysfunction in the inferior frontal junction (Schroeter et al., 2011). When similar executive function processes were assessed in MCI, a transitional diagnosis between normal aging and AD, multiple studies revealed deficits in planning (Brandt et al., 2009; Zhang et al., 2007), problem solving (Brandt et al., 2009), working memory (Brandt et al., 2009), switching (Crowell et al., 2002), and response inhibition (Traykov et al., 2007). While impairment in at least one cognitive domain is required for an MCI diagnosis, functional independence is thought to remain largely spared during this transitional period (Petersen, 1999). However, as a result of the significant role these executive function processes play in successful completion of day-to-day activities, it has been hypothesized that functional impairment may already likely exist at the time of an MCI diagnosis (Farias et al., 2006; Tuokko et al., 2005). While executive dysfunction is evident in the early stages of AD and MCI (Brandt et al., 2009; Crowell et al., 2002; Traykov et al., 2007; Zhang et al., 2007; Zheng

et al., 2012), these findings speak to the value of investigating this dysfunction prior to noticeable cognitive or functional impairment.

Less is known, however, about executive dysfunction in the preclinical or prodromal stages of AD. Indeed, AD disease progression is slow and is believed to begin years before symptoms become objectively apparent (Jack & Holtzman, 2013). One study revealed poorer executive function during the preclinical period of AD (Harrington et al., 2013), thereby demonstrating the predictive utility of assessing impairment within this domain in the future development of the disease (Albert et al., 2001; Ewers et al., 2014). Better understanding of executive dysfunction in nondemented older adults with an elevated risk for AD may be critical to differentiate individuals who will later progress to developing the disease.

Risk Factors for AD and the APOE ε4 Allele

While there is likely no singular cause for the development of AD, both modifiable and non-modifiable risk factors may increase susceptibility for disease development. Three of the most influential non-modifiable risk factors for late-onset AD include age, family history, and the Apolipoprotein-E ε4 allele (APOE ε4; Alzheimer's Association, 2018). Specifically, individuals 65 years or older are at an elevated risk for late-onset AD, with individuals 85 years or older at the greatest risk. However, having a first-degree family history of AD or at least one copy of the ε4 allele are also considered major risk factors (Saunders et al., 1993). Though individuals with any one of these risk factors are not guaranteed to develop AD, research has demonstrated that carriers of at least one of the ε4 alleles are at a three to four times increased likelihood (Farrer et al., 1997); thus, it is an especially important risk factor within the cognitive aging research.

As such, research has shifted toward evaluating the effects of the APOE ε4 allele on older adults prior to an AD diagnosis, particularly given the findings that these at-risk individuals show poorer performance in multiple cognitive domains (Small et al., 2004).

Executive Function in Individuals at Risk for AD

The existing literature regarding executive dysfunction in at-risk individuals prior to AD symptoms is small and inconsistent. One study demonstrated that cognitively intact older adults with a family history of AD performed significantly poorer on the Wisconsin Card Sorting Test (WCST) than individuals without a family history of the disease (Hazlett et al., 2015). When executive function performance was assessed alongside memory performance between ε4 carriers and non-carriers, asymptomatic carriers performed significantly below their non-carrier counterparts on the executive function task though not on the memory task (Luck et al., 2015). Similarly, facets of working memory implicated in executive function (Baddeley, 1992), such as goal maintenance, storage control, and interference control have shown to be negatively impacted by carrier status (Reinvang et al., 2010; Rosen et al., 2002). Using a spatial working memory task, Greenwood et al. demonstrated that individuals with two copies of the ε4 allele (ε4/ε4) showed reduced accuracy with increased memory load, a finding that was not as strong in heterozygous ε4 carriers (Greenwood et al., 2005). However, some studies have failed to find any significant executive function differences between cognitively intact ε4 carriers and non-carriers (Small et al., 2000; Smith et al., 1998).

Functional imaging studies have been relatively more consistent than behavioral measures pertaining to executive function in ε4 carriers. While Wishart and colleagues found comparable task performance between healthy ε4 carriers and non-carriers during

an auditory-verbal N-back task, task-related neural activation did reveal differences at the group level (Wishart et al., 2006). During the working memory task, fronto-parietal activation measured using functional-MRI (fMRI) revealed greater bilateral activation in ε4 carriers than in non-carriers (Wishart et al., 2006). This finding is consistent with the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, which posits that older adults reveal more symmetrical frontal activity than younger adults as a mechanism to compensate for cognitive aging (Cabeza, 2002). Other studies have reported increased neural activation in both frontal and parietal regions specifically during a low working memory load condition in ε4 carriers (Chen et al., 2013). Interestingly, in high working memory load conditions, activation was increased relative to low-load conditions in non-carriers but this difference was absent in carriers, revealing that ε4 carriers may have reached their capacity to recruit additional resources during the lower load conditions (Chen et al., 2013). This interpretation corresponds with the revised Scaffolding Theory of Aging and Cognition (STAC-r), which puts forth a theory similar to the HAROLD model, suggesting that older adults exhibit overactivation and increased neural recruitment, particularly in frontal regions, when compared to younger adults (Cabeza, 2002; Nielson et al., 2002; Reuter-Lorenz & Cappell, 2008). Han and Bondi contend that, similar to the HAROLD and STAC-r model, ε4 carriers demonstrate neural recruitment to compensate for declining cognition (Han & Bondi, 2008a), therefore masking dysfunction at a behavioral level.

With respect to the inconsistency within the literature, the varying tasks employed to assess executive function as a cognitive domain of interest is likely a contributing factor (Zheng et al., 2012). Frequently, executive function is used as a singular term in

the literature, though Miyake and colleagues have proposed that the three core executive functions (i.e., shifting, updating, and inhibition) are actually distinct processes with some underlying overlap (Miyake et al., 2000). As such, aspects of "executive function" are presumably affected differentially during AD disease progression and consequently, the measurement of certain processes may serve as better predictors of future cognitive decline than others.

Response Inhibition as a Specific Executive Process of Interest

The inhibitory control component of executive function is impaired early during the course of AD (Spieler et al., 1996) and in MCI (Johns et al., 2012), making it a particularly sensitive predictor. Inhibition can be described as the various mechanisms that underly an individual's ability to suppress irrelevant information and inhibit undesired responses (Hasher & Zacks, 1988; Logan, 1985). Three separable functions have been described as fundamental to inhibitory control: *access, deletion,* and *restraint* (Hasher et al., 1999; Lustig et al., 2007). The access function serves the purpose of de-cluttering incoming information so as to prevent irrelevant information from becoming the focus of attention. The deletion component eliminates irrelevant information that either the access function failed to filter or that was once relevant but no longer necessary to the current state. Lastly, the restraint component prevents prepotent but inappropriate responses to occur with the intent to allow other goal-direct responses to influence behavior (Hasher et al., 2007).

The restraint component, or response inhibition, is widely studied within the context of aging (Hasher & Zacks, 1988; Nielson et al., 2002; Spieler et al., 1996) and has demonstrated impairments in MCI and AD (Bélanger et al., 2010; Wylie et al., 2007).

Many studies using a go/no-go task, in which individuals are instruct to withhold a response to a no-go target, have demonstrated these deficits (Castiglioni et al., 2006; Crawford et al., 2005; Tripathi et al., 2015). However, the stop-signal paradigm is now favored as a measure of response inhibition, as it more closely mimics daily situations requiring a behavior to be unexpectedly inhibited (Rubia et al., 2003).

During a stop signal paradigm, a prepotent response tendency is created by instructing an individual to respond to all go targets as quickly as they can within a set time frame. However, less frequently, an auditory or visual stop signal is presented, in which case the individual is instructed to inhibit the prepotent response to the go target. This paradigm is based on the race model theory, which assumes performance is based on a "race" that takes place between the go and stopping process (Logan & Cowan, 1984). Successful response inhibition occurs when the process of stopping is quicker than the go process. If, however, the go process beats the stop process, the failure to stop results in a response being executed (Logan & Cowan, 1984). In contrast to tasks that measure reaction time through an overt behavior, successful stopping results in a response being inhibited, and therefore, the latency of this process cannot be directly observed. Thus, the latency is an estimate contingent upon the difference between the time at which the stop signal was presented (i.e., the stop signal delay) and the time at which the stopping process has finished (Logan & Cowan, 1984). While the stop signal delay is predetermined, the latter process is done by integrating the distribution of go signal reaction times until this equals the probability of responding given a stop signal is presented (Logan & Cowan, 1984). The result is a behavioral measure of response inhibition, or the stop signal reaction time (SSRT).

Research specific to the stop signal task has shown individuals diagnosed with AD exhibit slightly slower reaction times during the task when compared to normal elders (Amieva et al., 2002), as well as more stop failures (i.e., commission errors; Amieva et al., 2002; Amieva et al., 2004). Individuals diagnosed with amnestic MCI also showed less efficient response inhibition during a stop signal task, with these individuals exhibiting slower SSRT than normal controls (Zheng et al., 2012).

Less is known about the specific effects of the ε4 allele on response inhibition. To the best of our knowledge, only one study has thus far examined response inhibition in carriers and non-carriers; the measure of inhibition was the Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (DKEFS; Wetter et al., 2005). The investigators found that cognitively intact carriers of the ε4 allele demonstrated poorer performance on the inhibition/switching condition of the CWIT, a condition that requires both response inhibition and switching processes. Given the mixed results within the executive function literature, with more consistent findings using imaging techniques than behavioral measures, and the single study related to response inhibition in ε4 carriers, functional imaging techniques may be important to furthering our understanding of early indicators of cognitive aging and decline.

Functional Neuroimaging: Electroencephalography

Currently, there are many available functional imaging methods that have allowed cognitive aging researchers to better explore the relationship between cognitive and neural changes during the aging process. Functional-MRI is one method that has been most frequently used within the field and provides excellent localization power, though this is at the expense of temporal power. This technique relies on an indirect method of

measuring neuronal activity (Logothetis, 2008) by using blood oxygenation level-dependent (BOLD) imaging; this method operates under the assumption that increased blood flow is required for more active brain regions. The hemodynamic response, however, is several seconds slower than the neuronal signal, resulting in low functional temporal resolution. While this may be considered one of the bigger disadvantages of fMRI, it is also costly and is accompanied by inconvenient exclusionary criteria such as having a pacemaker, aneurysm clip, surgical devices, and claustrophobia. These criteria pose difficulty, particularly for an aging population, as many older adults fail to meet inclusion criteria and, thus, are unable to undergo fMRI.

Unlike functional imaging techniques that measure neural activity indirectly, electrophysiological methods are relatively inexpensive and non-invasive ways to directly measure activity, providing excellent temporal resolution (Cohen, 2014). Electroencephalography (EEG) uses electrodes placed directly on the scalp to record fluctuations in the electrical potential, or voltage, produced by the synchronous firing of neural populations in the cerebral cortex (Cohen, 2017). These voltages produced are very small, and therefore, each electrode is connected to an amplifier allowing for the visualization of the voltage signal produced by the brain (Luck, 2012).

Event-related Potentials

Studies frequently use event-related potentials (ERPs), an application of EEG, to investigate cognitive processes, including response inhibition. When an epoch of EEG is time-locked to a specific stimulus, the voltage changes generated by this specific event or stimulus is considered an ERP (Coles & Rugg, 1995). However, relative to the EEG waveform, the ERP is small, thus requiring additional signal processing techniques to

separate the ERP from the background EEG (Coles & Rugg, 1995; Luck, 2012). Consequently, many EEG epochs are recorded and averaged, generating an average ERP waveform. The background EEG varies randomly across epochs, allowing for the ERP to be extracted and temporally related to an event of interest, while the background EEG averages to zero (Coles & Rugg, 1995).

The ERP waveform consists of voltage deflections that create both positive and negative peaks or components (Luck, 2012). These components are described by certain features, including the polarity and latency (Luck, 2012). The polarity, labeled using a P or an N, describes whether the peak of interest is positive or negative going, respectively. A peak can also be described by its latency post stimulus onset in milliseconds within a waveform. For example, both P300 and N200 are peaks frequently observed in the waveform, with the former being a positive going wave observed around roughly 300 milliseconds (ms) following stimulus onset and the latter being a negative going wave observed around 200 ms following stimulus onset. Though polarity and latency are used to label the peak of interest within the waveform, other features of the ERP such as scalp distribution and amplitude are also used to describe the waveform within the literature (Coles & Rugg, 1995; Luck, 2012).

ERP Components Reflecting Response Inhibition

One component that is regularly discussed within the context of response inhibition is the N200 wave. This component has most classically been observed as a result of random deviations in more frequent stimuli, oftentimes measured using an oddball paradigm (Folstein & Van Petten, 2008). Specific to the oddball task, the N200 amplitude is observed to be larger when improbable events occur when compared to the

more probable occurring stimuli. As such, the N200 within this context has been interpreted as a reflection of conflict monitoring (Donkers & Van Boxtel, 2004; R J Huster et al., 2010). Based on the findings using an oddball paradigm, tasks requiring response inhibition have also been used to better understand the N200 component. For example, when go trials are more frequent than no-go trials during a go/no-go paradigm, a larger N200 amplitude during no-go trials has been demonstrated (Luck, 2012). This may reflect the produced conflict generated by the infrequent no-go trials and more frequent go trials. Topographically, the N200 component during no-go trials is most pronounced at frontal and central electrodes (Sasaki et al., 1993). Similar to go/no-go tasks, the N200 component is also observed during stop signal tasks. When a stop signal paradigm is used, the N200 component is observed to be larger when participants make a commission error (i.e., stop failure) than when they are successful in stopping (Roberts et al., 1994; van Boxtel et al., 2001). This reflects the race model, where conflict should be greatest when the go process beats out the stopping process (Roberts et al., 1994; van Boxtel et al., 2001).

The P300 component, suggested to represent updating of working memory (Donchin & Coles, 1988) and attentional processes (Kramer & Strayer, 1988) is also observed during response inhibition tasks. Differential behavior of the P300 peak has been demonstrated when go and no-go trials are compared. During go trials, this component is largest at posterior regions (Bokura et al., 2001). However, during trials requiring inhibition (i.e., no-go), an “anteriorization”, or shift from a more posterior to an anterior scalp distribution, is often observed (Bokura et al., 2001; Roberts et al., 1994). The stop signal paradigm has also resulted in a similar topographical pattern as the N200

component. While go and stop trials elicit a comparable P300 wave at parietal electrodes, it is observed at its largest at frontally and centrally located electrodes during stop trials (van Boxtel et al., 2001). The N200 and P300 component frequently observed together during tasks measuring response inhibition, sometimes referred to as the N2/P3 complex (Falkenstein et al., 2002).

ERP as a Biomarker

Studies using ERPs to investigate response inhibition have demonstrated differences in the N200 and P300 components in individuals diagnosed with MCI and AD. Both the N200 and P300 components have exhibited reduced amplitudes in participants diagnosed with MCI during a flanker task, a task that measures response inhibition and conflict resolution (Wang et al., 2013). In the same study, an even greater reduction in N200 and P300 amplitude was observed in those with AD when compared to those with MCI and healthy controls (Wang et al., 2013). Likewise, research using a go/no-go task showed reduced N200 amplitude in individuals with MCI (Cid-Fernández et al., 2014). Although these authors found no differences in the P300 component between the MCI and the healthy control group (Cid-Fernández et al., 2014), other studies using a go/no-go task have demonstrated reduced P300 amplitudes, interpreted as impaired response inhibition (López Zunini et al., 2016). While studies using ERPs elicited during inhibitory tasks have shown utility in differentiating individuals with and without cognitive impairment, little is known regarding ERPs in cognitively intact population at an increased risk for AD.

The existing literature focused on an at-risk population does, however, support a link between modulated electrophysiology and increased risk. During an auditory oddball

task, individuals with a family history of AD exhibited prolonged N200 and P300 latencies (Green & Levey, 1999). When the effects of the APOE4 ε4 allele were investigated, it was observed that the N200 amplitude may be particularly vulnerable to this risk factor in persons with MCI (Reinvang et al., 2005). Specifically, MCI participants carrying at least one ε4 allele exhibited reduced N200 amplitudes during an oddball task (Reinvang et al., 2005).

EEG Neural Oscillations as a Complementary Method to ERP Research

Research has begun to extend the EEG literature beyond ERPs by using time-frequency analyses so as to better capture neural activity not visible using the ERP approach (Regel et al., 2014; Sauseng & Klimesch, 2008). As such, many studies are now focused on neural oscillations allowing for the investigation of event-related synchronization (elevated power) and desynchronization (reduced power) assumed to be directly related to the increased or decreased firing of neuronal populations in response to specific stimuli or events. This approach can be viewed as complementary to ERP research while simultaneously providing the potential to observe neural "signatures" or modulation that can be directly linked to certain cognitive processes of interest (Albares et al., 2015). Relatedly, due to the subtlety of the cognitive alterations during the course of AD disease progression, examining event-related EEG oscillations can serve as a more sensitive approach to identifying these early alterations, particularly in a task measuring response inhibition.

Neural oscillations are described by the speed of the oscillation (frequency) and the position along a sine wave at any point in time (phase; Cohen, 2014). Typically, oscillatory activity is divided into five main bands based on frequency; slow frequencies

including delta (3 Hz and below), theta (4-8 Hz), and alpha (8-12 Hz), and fast frequencies including beta (12-22 Hz), and gamma (above 22 Hz). Modulation in power, or the squared magnitude of the amplitude, within these frequency bands observed during tasks can be compared to a pre-stimulus baseline period and has been linked to different functions and neural information processing (Mathalon & Sohal, 2015). These neural processes include motor, functional, emotional, and cognitive, though, less is understood regarding the distinct role or process associated with each individual frequency band (Engel & Fries, 2010).

Motor-related Beta Activity

The beta frequency band remains one of the least understood bands within the EEG literature and is most classically linked to motor function (Neuper & Pfurtscheller, 2001). This band is primarily observable over the sensorimotor cortices and is most prominent during the activation of these regions (Pfurtscheller, 1981). It is well established that beta activity changes as a function of movement, with beta power being at its lowest *during* the execution of a motor response and its highest *after* a movement (Salmelin et al., 1995).The latter elevation in post-movement beta power is commonly referred to as the beta "rebound", and typically occurs around 300 to 1000 ms after a movement has terminated (Kilavik et al., 2013). Beta activity specific to movement is commonly explored in inhibitory tasks such as the stop signal and go/no-go tasks as these tasks typically require a motor response or withholding of a motor response. However, accumulating evidence demonstrates that the role of beta may extend beyond motor function, as beta activity is observable in other cortical areas, including the frontal region

(Huster et al., 2013; Swann et al., 2009). As such, its activity has gained considerable attention with respect to extensive cognitive processes.

Cognitive-related Beta Activity

Non-motor related beta activity has been associated with a number of processes relating to top-down neural signaling (Hwang et al., 2014) and executive function, including working memory (Babiloni, Babiloni, Carducci, Cincotti, et al., 2004), interference control (Tafuro et al., 2019; Zavala et al., 2017), and response inhibition (Huster et al., 2013; Swann et al., 2009). Specifically, beta band activity during working memory is particularly relevant when suppression of distractor or irrelevant information is necessary. For example, an elevation in prefrontal beta during a delay period may serve the purpose of preserving the current working memory state or protecting its contents from interference (Schmidt et al., 2019). Zavala and colleagues used intracranial EEG recordings and revealed reduced beta power in the lateral prefrontal cortex during a non-motor decision making task (Zavala et al., 2017). This reduction in beta power, however, was significantly attenuated when participants were required to ignore distractor stimuli (Zavala et al., 2017). As such, beta activity has been theorized as an inhibitory filter for working memory, particularly when distractors are present or the prevention of encoding is necessary (Miller et al., 2018; Zavala et al., 2017).

Beta band activity may also play a central role in communication within the fronto-basal-ganglia network, the neural network implicated in response inhibition (Aron et al., 2014; Swann et al., 2009). As such, a recent surge in research has shown that successful stopping is uniquely associated with elevated beta power at frontal and centrally placed electrodes (Alegre et al., 2008; Krämer et al., 2011; Swann et al., 2009;

Wagner et al., 2018). This research was further supported by a study using intracranial EEG, revealing that an increase in beta power, elicited by successful response inhibition, was specific to the right inferior frontal cortex (Swann et al., 2009), a region particularly critical for inhibitory control (Aron et al., 2003, 2014). Along these lines, Castiglione and colleagues found elevated beta activity at right frontal electrodes during a think/no-think task, indicating that movement-related (i.e., stop signal task) and cognitive-related (think/no-think) stop paradigms elicit common underlying neural activity (Castiglione et al., 2019). These findings further underscore the relevance of beta beyond solely motor-related processes, as beta activity may serve as a marker of inhibitory control.

Beta Band Activity as a Sensitive Biomarker

There remains a dearth of research examining inhibitory control-related beta activity in populations diagnosed with cognitive impairment, such as MCI and AD. However, it is well-established that a decrease in beta spectral power is associated with the presence of AD (Holschneider & Leuchter, 1995). Indeed, beta-band desynchronization measured at rest has been associated with greater impairment in patients with AD and MCI (König et al., 2005). This decrease in beta activity may be a potential factor underlying impaired response inhibition in persons with MCI (Tan et al., 2019).

While little research exists specifically examining task-related beta activity in AD and MCI during response inhibition tasks, differing beta-band profiles have been demonstrated in these populations using other measures, including working memory tasks. For example, one study reported reduced amplitude of beta event-related synchronization during a 2-back task in AD and those with progressing MCI, compared

with elderly controls and those with stable MCI (Missonnier et al., 2007). Similarly, reduced beta event-related synchronization has been shown during a Sternberg working memory task (i.e., similar to an n-back task) in those with MCI when compared with elderly controls (Fodor et al., 2018). Another study using this task showed a similar reduction in beta activity in individuals with AD, but no difference was evident between those with MCI and elderly controls (Kurimoto et al., 2012). While these tasks differ from the tasks that more closely measure response inhibition, the ability to clear working memory of irrelevant information has been shown to decline with age and remains an important aspect of inhibition (Hasher & Zacks, 1988). Furthermore, tasks requiring working memory and inhibition may involve similar neural components, particularly the right inferior frontal gyrus (McNab et al., 2008). Deficits in these shared components, therefore, may play a role in the reduced beta power exhibited in individuals with MCI an AD during working memory tasks. These studies suggest that modulated task-related beta activity accompanies cognitive impairment, irrespective of the executive function task used.

A critical next step within the literature is to extend the current research pertaining to task-related beta activity in cognitively impaired elders to a population of cognitively intact elders at an increased risk for AD. However, of the limited EEG studies looking at the influence of the ε4 allele on beta activity, the literature is based almost entirely on resting-state data (Babiloni et al., 2006; Jelic et al., 1997; Koelewijn et al., 2019; Kramer et al., 2008; Lehtovirta et al., 1996). For example, Lehtovirta and colleagues found reduced resting beta power in ε4-carriers, although this study took place in a population already diagnosed with AD (Lehtovirta et al., 1996). In contrast, one

study reported no differences in resting beta power between cognitively intact ε4-carriers and non-carriers; resting differences were apparent only in the alpha band (Babiloni et al., 2006). Extrapolation of the current resting-state EEG research to event-related oscillatory activity will further interrogate the relationship between neural and cognitive processes in a nondemented, at-risk, older adult population.

The Present Study

Studies have shown an association between the ε4 allele and poorer neuropsychological scores and/or increased neural activation during tasks relating to executive function (Chen et al., 2013; Reinvang et al., 2005; Rosen et al., 2002; Wishart et al., 2006). However, there is a general lack of consensus regarding executive function in cognitively intact ε4 carriers, and there has been very little study of the effects the ε4 allele has on specific executive function processes, such as response inhibition (Wetter et al., 2005). While neuropsychological or behavioral performance on tasks of executive function/inhibition may lack the sensitivity to detect subtle differences in cognitively intact, at-risk individuals, neural activity may better differentiate between individuals who are most likely to develop AD. Electrophysiological methods, such as ERP and EEG studies have investigated neural activity related to the ε4 allele (Babiloni et al., 2006; Green & Levey, 1999; Lehtovirta et al., 1996; Reinvang et al., 2010), however, few studies have examined the differences in these neural markers between cognitively intact older adult carriers and non-carriers.

The present study examined EEG oscillatory activity as a biomarker to target these gaps in the existing literature. As such, cognitively intact, older adult ε4 carriers and non-carriers underwent electrophysiological recording during a stop signal task.

Behavioral performance and neural activity specific to response inhibition was assessed. Specifically, event-related beta activity was investigated in carriers and non-carriers during a stop signal task, consistent with the current literature positing that beta activity is implicated in the process of response inhibition and top-down neural processing (Hwang et al., 2014). The long-range goal is to move the literature toward examining the utility of beta band EEG as a prodromal marker of cognitive decline.

Hypotheses

Hypothesis 1. The current literature demonstrates that an increase in task-related frontal beta-band power during tasks of attention and working memory may be related to interference control compared to the relatively low beta power observed during an encoding phase (Miller et al., 2018; Schmidt et al., 2019; Zavala et al., 2017). Moreover, research has suggested that an increase in beta-band power is observed at frontal electrodes when successful stopping or response inhibition takes place during a stop signal, go/no-go, and think/no-think task (Alegre et al., 2008; Castiglione et al., 2019; Krämer et al., 2011; Kühn et al., 2004; Swann et al., 2009; Wagner et al., 2018). In line with this research, it was expected that elevated beta activity would be observed at frontal electrodes across groups (i.e., in both carriers and non-carriers of the ε4 allele) in stop conditions relative to go conditions during a stop signal paradigm.

Hypothesis 2. In keeping with the compensatory theory of aging (STAC-r), the research examining the compensatory theory in response inhibition (Cabeza, 2002; Nielson et al., 2002; Reuter-Lorenz & Cappell, 2008), and the suspected compensatory mechanisms employed by carriers of the ε4 allele due to declining neural integrity (Chen et al., 2013; Han & Bondi, 2008b; Wishart et al., 2006), it was hypothesized that ε4

carriers would reveal greater frontal beta-band power than non-carriers during successful stop trials. Greater frontal beta power in carriers would be employed as a compensatory strategy due to declining cognition in order to maintain task accuracy.

Hypothesis 3. Consistent with research that suggests beta power plays a critical role in successful response inhibition (Huster et al., 2013; Swann et al., 2009) and the STAC-r model (Reuter-Lorenz & Cappell, 2008), it was hypothesized that greater beta power (i.e., increased neural recruitment) during stop trials at frontal electrodes would be positively associated with SSRT. The SSRT may reflect task difficulty, with slower SSRT reflecting more difficulty to complete the task successfully.

Hypothesis 4. Lastly, it was predicted that the role of beta may extend beyond response inhibition and may relate to more general executive function processes (Babiloni, Babiloni, Carducci, Cappa, et al., 2004; Hwang et al., 2014; Tafuro et al., 2019; Zavala et al., 2017). As such, it was expected that beta band power at frontal electrodes would be negatively associated with task performance on traditional neuropsychological tests that measure executive function.

Method

Participants.

Participants were recruited via newspaper advertisement from the local Milwaukee area for a previous larger-scale study of cognitive aging. Forty-six cognitively intact older adults (M_{age} = 77.40, *SD* = 4.86), 24 of whom were carriers of least one of the APOE ε4 alleles, underwent EEG data collection. Cognitive status was assessed with an

initial phone screener and cognitive battery including the Mini Mental State Examination (MMSE; Folstein et al., 1975) and Mattis Dementia Rating Scale-2 (DRS-2; Jurica et al., 1988). Older adult participants were compensated monetarily. Young adult participants were recruited and volunteered through the Psychology Subject Pool; they were enrolled as undergraduates at Marquette University. Young adult (M_{age} = 19.9, SD = 2.72) data were used as a reference group for post-hoc analyses. All procedures were approved by the Marquette Institutional Review Board.

Measures.

Mattis Dementia Rating Scale – Second Edition (DRS-2). The present study used total DRS-2 (Jurica et al., 1988) score in order to screen for potential cognitive impairment in our older adult sample. The measure assesses five cognitive domains, including attention, initiation and perseveration, construction, conceptualization, and memory. A DRS-2 cut-off score of 130 was used as an indication of intact cognitive ability (Monsch et al., 1995).

The Stop-Signal Task. The Stop-Signal task measures response inhibition, an integral part of executive control (Logan, 1985). Participants must inhibit the over-learned behavior of responding to a stimulus when new rules are defined and applied. This task is sensitive to right inferior frontal gyrus activation when successful stopping takes place (Aron et al., 2007). As such, an increase in activation in this brain region is negatively correlated with SSRT (Aron & Poldrack, 2006; Rubia et al., 2007). Performance on the stop signal task is computed using a go and stop signal task. These tasks were administered via computer and presented in MATLAB (version 7.12, MathWorks).

During the go task, participants were presented with either an “r” or “s” stimulus in black ink against a light grey background on a computer monitor. Letters were presented at a rate of 750 milliseconds per letter with an inter-stimulus interval of 0 milliseconds. Individuals were instructed to press the spacebar every time an “r” or “s” appears on the monitor screen, which sets up a prepotent response (go condition).

During the stop task, participants were presented with either an “r” or “s” in black ink. Letters were again presented at a rate of 750 milliseconds per letter with an inter-stimulus interval of 0 milliseconds. Similar to the go task, individuals were instructed to press the spacebar every time an “r” or “s” appears on the monitor screen (go condition), however, participants were also instructed to inhibit this response to a go target if it is interrupted by a stop signal (stop condition). This stop signal is a red screen that flashed for 100 milliseconds after the “r” or “s” stimuli appeared. The stop signal appeared either 125 milliseconds (i.e., easier) or 200 milliseconds (i.e., harder) after the “r” and “s” stimuli were presented. This approach was used to provide sufficiently high task accuracy to allow sufficient inhibitory trials to be analyzed; only correct trials included in EEG analyses.

For this task, practice trials (2 blocks) were administered prior to the test blocks. Participants first became familiar with the task instructions during the first practice block; this block presented stimuli at a rate of 1000 milliseconds per stimulus. After participants become acquainted with the task, a second practice block was administered at the same speed as the test blocks. During task completion, a rest break (20-seconds) was used to remind participants of instructions and to separate each testing

block into three smaller parts; this task set-up was used to control for fatigue during the task.

Genetic Testing: Apolipoprotein E Allele. APOE genotyping was performed using genetic material from a mouth swab (i.e., buccal cells; Hixson & Vernier, 1990; Saunders et al., 1993) using Sample to SNP kits (Applied Biosystems, Foster City, CA). DNA for APOE genotyping was performed using TaqMan assays (ABI) in as large batches as possible given the timeline, with known genotyped controls run with each batch. Specifically, for APOE allele determination, two separate SNP genotyping using the polymorphisms rs7412 and rs429358 in order to distinguish between alleles (i.e. ε2 /ε4, ε3/ε3, ε3 /ε4 and ε4/ε4). Those with ε3/ε4 or ε4/ε4 were deemed ε4-positive; all other allele combinations were deemed ε4-negative.

Behavioral Analysis (SSRT). For the stop signal task, go reaction time (RT) and SSRT were calculated for each participant. The go RT is a measure of completion time when no stop signal was present and a prepotent motor response does not need to be inhibited. SSRT was calculated using the integration method. This method collapsed all the go signal RT on which no stop signal occurred into a signal distribution. The number of RTs in the distribution (*m*) was multiplied by the probability of responding at a given delay. From this calculation, *n* is obtained. The RTs were then ranked, and the *n*th RT was selected, which estimates the time at which the process of stopping was complete, relative to the go signal onset. The stop signal delay was then subtracted from this value. This process was completed for each stop signal delay for each participant. Results were averaged for each participant, in which the SSRT was obtained (Logan & Cowan, 1984).

EEG data acquisition. EEG data were collected using a 64-channel Neuroscan SynAmps2 system with active electrode actiCAP (Brain Products). Electrodes on the actiCap were arranged according to the extended international 10-20 system with a reference at FCz and a ground at AFz and impedances kept under 50 kΩ. The distance between adjacent electrodes was either 10% or 20% of the total distance from the front to the back (nasion to inion) or right to left (right to left preauricular points anterior to the ear) of the skull. The EEG was recorded 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 Processing and Analysis.

EEG data analysis was performed using BrainVision Analyzer2 (Brain Products). The data was downsampled to 256 Hz. In order to eliminate channel-level artifacts, channels which were especially noisy were rejected as necessary. Data for rejected channels were interpolated based on the average of surrounding electrodes. This step was completed prior to re-referencing the data so as to not impact the average reference. After this step, preprocessing procedures were consistent with other participants and are as follows. First, the data was re-referenced during off-line analysis to a common average of all electrodes. Second, the data was high-pass filtered at 0.1 Hz (zero phase shift Butterworth filter, order 2) to minimize slow drifts, and low-pass filtered at 100 Hz (zero phase shift Butterworth filter, order 2) with a notch-filter of 60 Hz. Third, ocular correction was performed using Gratton and Coles algorithm as implemented in the Analyzer software. Fourth, EEG artifacts were automatically inspected and rejected as follows: any abrupt change in voltage during the 100 ms prior to and post-stimulus onset, any difference of values in 200 ms intervals that exceed 200 μV, any amplitude (positive

or negative) that exceeds 150 μV during the 200 ms prior to and post-stimulus onset, and any activity that was consistently smaller than 0.5 μV during a 200 ms interval were considered artifacts and the appropriate segments were rejected for all channels. Fifth, the continuous EEG data were visually inspected to reject gross artifacts that the automatic algorithm might have missed. Sixth, for both correct go and stop trials, these data were epoched from 200 ms prior to stimulus onset to 800 ms after stimulus onset. Error trials were excluded from analysis to limit error or task difficulty related neural response. Epochs were averaged separately for correct go and stop trials.

Time-frequency analyses of event-related EEG data were performed using Fast Fourier Transform algorithm for correct go and stop trials (Hanning window length of 15%). Power estimates were derived from the average for the beta (14-30 Hz) frequency band at Fz, FCz, Cz, CPz, and Pz electrode sites (see Figure 1). Grand average power for beta frequency during correct go and stop trials were calculated across participants based on gene status.

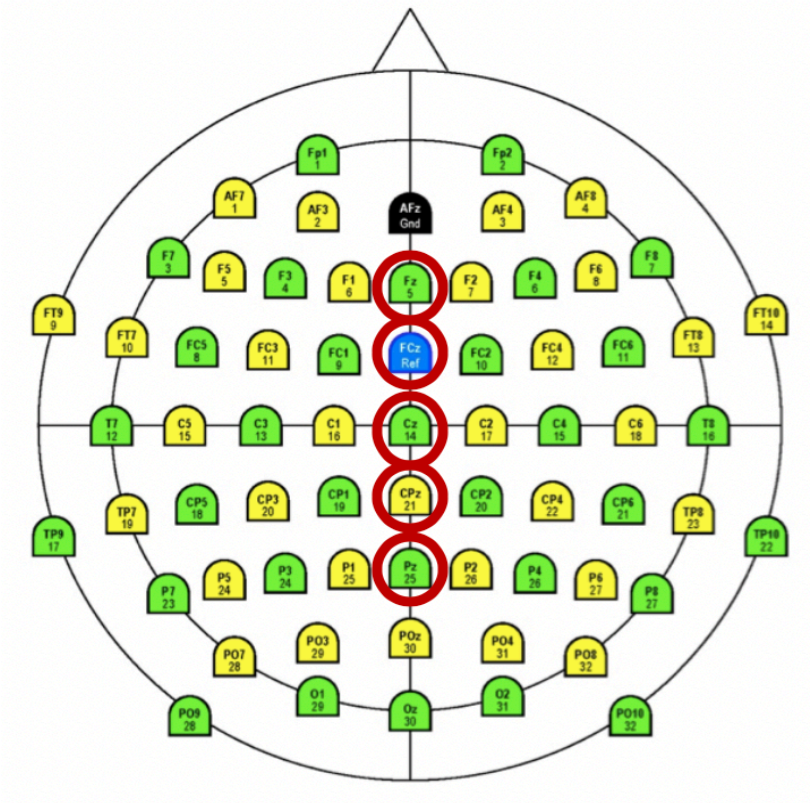

Figure 1. Electrode placement on 64-electrode Brain Products actiCAP arranged according to the extended international 10-20 system. Electrodes of interest for current analyses are circled in red (Fz, FCz, Cz, CPz, Pz).

Procedures.

EEG time-frequency data during the stop signal task were collected as part of a larger multi-task study. Study participants completed two testing sessions that were approximately one week apart. The informed consent process was completed during the initial part of each testing session. The first testing session included completion of neuropsychological testing, including the DRS-2 and MMSE used as cognitive screeners. EEG data were collected during the second session, where participants completed the stop signal task. During this task, participants were seated comfortably in front of a computer screen, and the EEG cap was placed on their head. All participants were

instructed to limit gross motor movement during the task so as to reduce noise in the EEG signal. Instructions were read aloud to the participant as they appeared on the computer screen; participants were given a change to ask question regarding the task. The stop signal task was presented in MATLAB (version 7.12, MathWorks).

Results

Excluded Data.

Two participants (2 APOE ε4-) were excluded from all analyses upon visual inspection of EEG data. As a result, the final sample included 44 cognitively intact older adults (21 APOE ε4+, 23 APOE ε4-). Risk groups did not significantly differ by age, sex, or DRS-2 score. Years of education did significantly differ between risk groups ($t(42) = -2.20$, $p = .033$), with ε4+ having greater educational attainment than ε4-. As this is expected to reduce group differences as a protective effect in ε4+, education was not covaried in subsequent analyses. Sample demographics are presented in Table 1.

Table 1.
Sample Demographics (mean (± SD))

	Total Sample (n = 44)	APOE ε4+ (n = 21)	APOE ε4- (n = 23)
Age (years)	79.73 (4.8)	78.96 (4.4)	80.42 (5.0)
Education (years)	14.93 (2.6)	15.81 (3.1)*	14.13 (1.8)*
Sex (% female)	75.0%	81.0%	70.0%
DRS-2 (total)	138.57 (3.0)	137.95 (3.3)	139.13 (2.6)

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

Behavioral Data Analyses.

Differences in accuracy and response latency between APOE ε4+ and APOE ε4- older adult participants was assessed using a serious of independent sample t-tests. There were no differences in accuracy between risk group in Go PCTT ($t(42)=-.146$, $p=.885$), Stop PCIT ($t(42)=.676$, $p=.503$), Stop PCTT ($t(42)=.717$, $p=.478$) or in response latency between risk group in Go RTT ($t(42)=-1.02$, $p=315$) and Stop SSRT ($t(41)=-.443$, $p=.660$).

Table 2.
Descriptive Statistics for Behavioral Variables (mean (± SD))

	Total Sample (n = 44)	APOE ε4+ (n = 21)	APOE ε4- (n = 23)
Accuracy			
Go PCTT	99.49 (.84)	99.51 (.95)	99.47 (.74)
Stop PCIT	74.94 (11.73)	73.68 (14.58)	76.09 (8.53)
Stop PCTT	98.54 (2.68)	98.24 (3.61)	98.82 (1.42)
Response Latency			
Go RTT (ms)	680.31 (45.7)	687.64 (48.3)	673.62 (43.2)
Stop SSRT (ms)	540.70 (37.8)	543.30 (34.5)	538.2 (41.2)

Note: APOE = Apolipoprotein-E; PCTT = Percent Correct Target Trials; PCIT = Percent Correct Inhibitory Trials; RTT = Reaction Time to Targets; SSRT = Stop Signal Reaction Time. There were no significant genetic risk group differences in accuracy or response latency.

Time-frequency Analyses.

Condition (Go vs. Stop). A 2x5 repeated measures ANOVA was used to analyze beta power differences between *Condition* (Go/Stop) and at *Electrode Site* (Fz, FCz, Cz,

CPz, Pz) during a stop signal task. Results showed a significant main effect of *Condition* ($F(1,43) = 5.20$, $p = .028$). Pairwise comparisons revealed beta power was significantly greater during correct go trials compared to correct stop trials. Although an *Electrode Site* main effect did not reach significance, results revealed a trend toward significance ($F(1,172) = 2.17$, $p = .074$). Pairwise comparisons showed significantly greater beta power at the Fz electrode site when compared to FCz ($p < .001$) and Cz ($p = .018$) electrode sites. The *Condition* x *Electrode Site* interaction did not reach significance ($F(1,172) = 1.73$, $p = .145$), although visual inspection showed somewhat greater beta power at Fz in the correct stop condition when compared to correct go condition, which was predicted (see Figure 2).

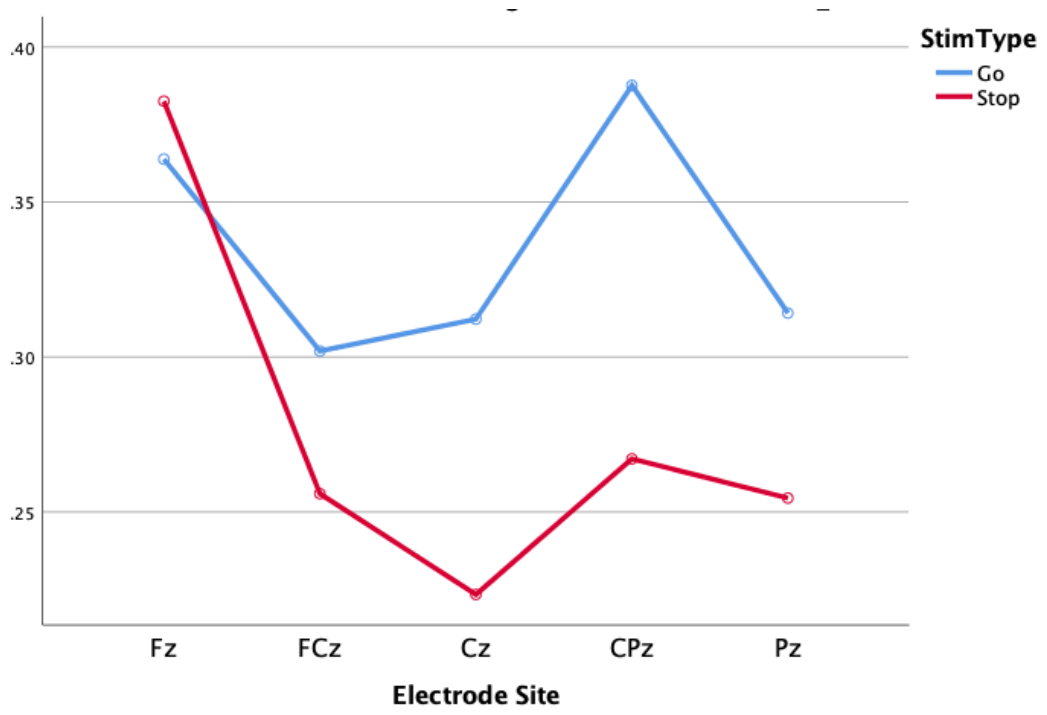

Figure 2. Beta power by task condition (correct Go vs. correct Stop) at Fz, FCz, Cz, CPz, and Pz electrode sites. There is a slight elevation in beta power at the Fz electrode site in the stop condition compared to the go condition.

As a result of the slight elevation in beta power at the Fz electrode site in correct stop trials compared to correct go trials, a post-hoc 2x3 repeated measures ANOVA was used to further capture the frontal beta effect during correct stop trials. Beta power differences between *Condition* (Go/Stop) and *Sites* where an average of the frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrode sites was used (see Figure 3), were further investigated. Results of interest include a main effect of *Location* ($F(2,86) = 11.60$, $p < .001$); pairwise comparisons revealed significantly greater beta power at frontal compared with central ($p = .045$) and parietal ($p < .001$) sites, and greater beta power at central compared with parietal sites ($p = .001$). Most notably, the *Condition* x *Sites* interaction was also significant ($F(2,86) = 5.72$; $p = .005$), with pairwise comparisons revealing significantly greater beta power at the frontal site in the stop condition when compared to the go condition ($p = .008$).

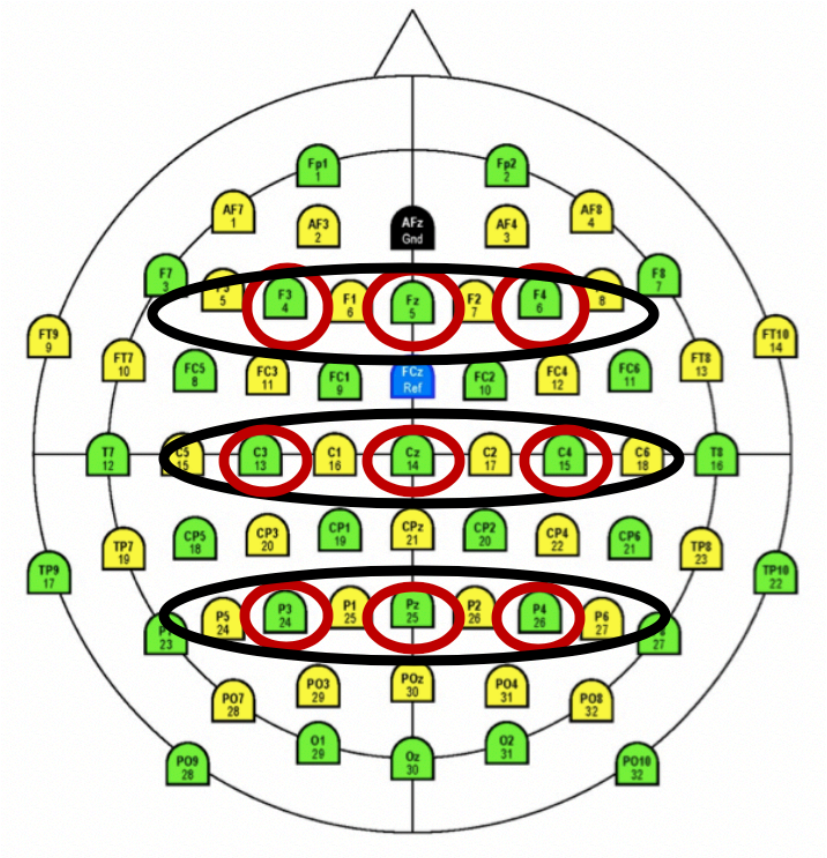

Figure 3. Electrode placement on 64-electrode Brain Products actiCAP arranged according to the extended international 10-20 system. Electrodes of interest for post-hoc analyses are circled in red. Clustered electrodes are circled in black and were averaged together to create a frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) region of interest.

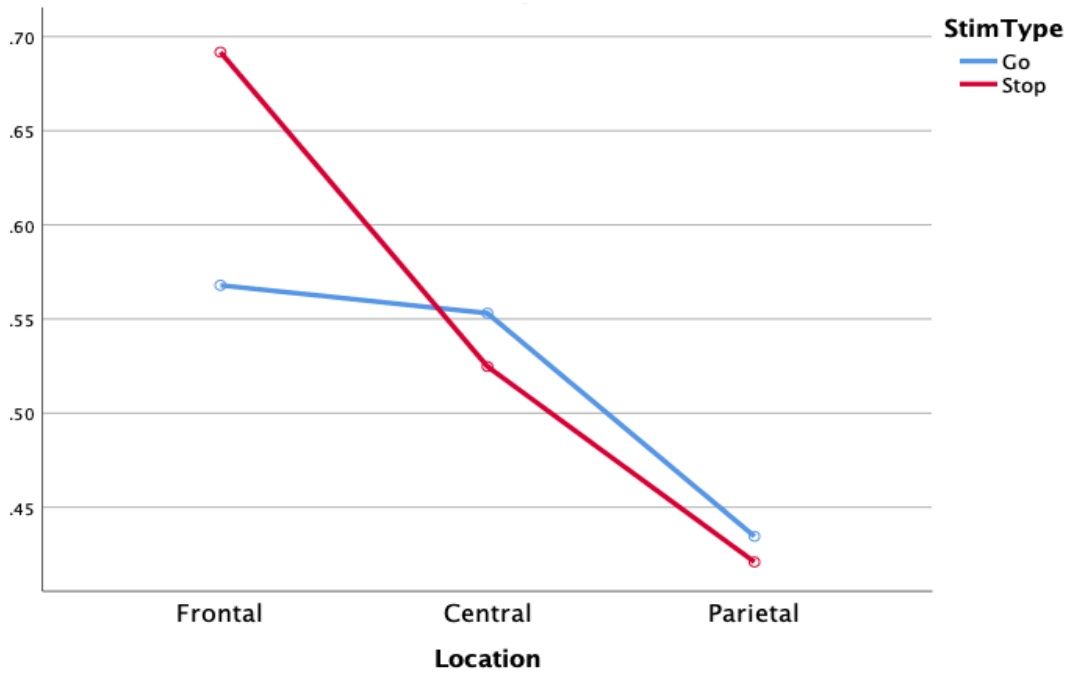

Figure 4. Beta power by condition (Go vs. Stop) at frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrode sites. Beta power was elevated at the frontal electrode site in correct stop condition.

Genetic Risk Groups (ε4+ vs. ε4-) during Stop. A 2x5 mixed ANOVA including *Risk Group* (APOE ε4+/APOE ε4-) and *Electrode Site* (Fz, FCz, Cz, CPz, Pz) assessed beta power differences between gene group during the stop condition of a stop signal task. The main effect of *Electrode Site* was significant ($F(4,168) = 4.76$, $p=.001$), with pairwise comparisons showing beta power at the Fz electrode significantly greater than beta power at the FCz, Cz, CPz, and Pz electrode sites. Although the *Risk Group* x *Electrode Site* interaction did not reach significance ($F(4,39) = .79$, $p=.532$), visual inspection showed that mean beta power was slightly greater at the Fz electrode site in ε*4+* group compared to the ε*4-* group, which was predicted (see Figure 5).

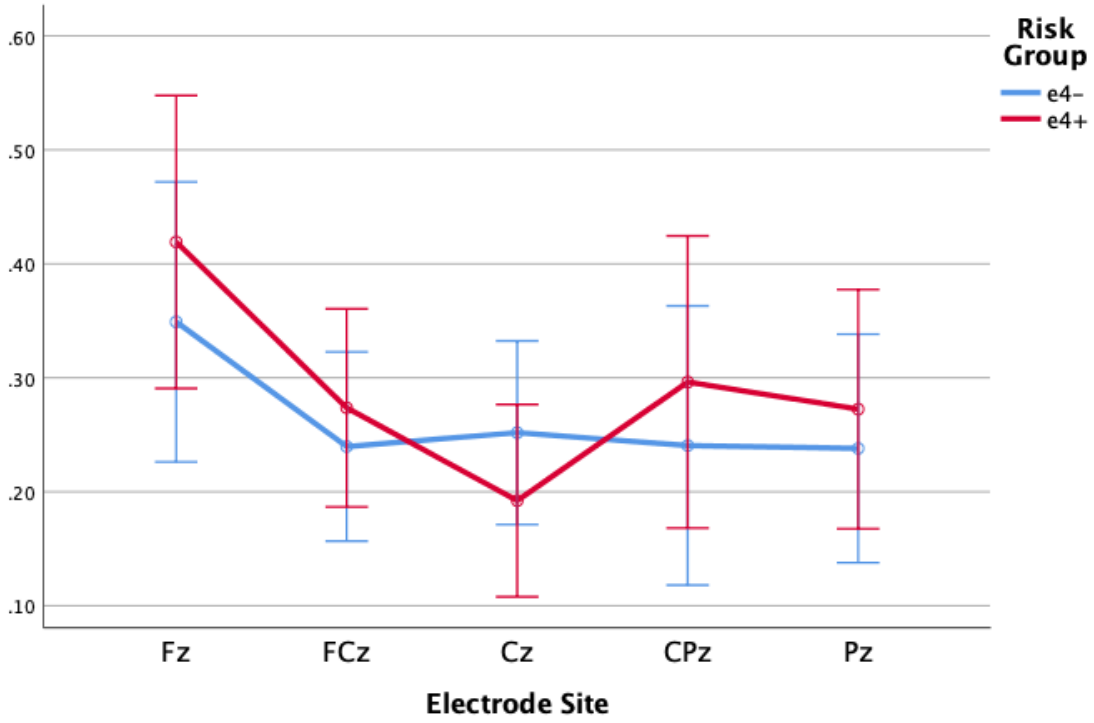

Figure 5. Beta power by risk group (ε4- vs. ε4+) at Fz, FCz, Cz, CPz, and Pz electrode sites. Beta power is slightly elevated at the Fz, CPz, and Pz electrode sites in ε4+ risk group.

Post-hoc analyses were performed so as to further examine beta power differences specifically at frontal electrodes between ε*4*- and ε*4*+ carriers during correct stop trials. A 2x3 mixed ANOVA including *Risk Group* (APOE ε4+/APOE ε4-) and *Frontal Electrode Site* (F3, Fz, F4) revealed a significant main effect of *Electrode Site* ($F(2,84) = 23.09$, $p < .001$). Pairwise comparisons revealed greater beta power at the left and right frontal electrode site (F3/F4) when compared to the fronto-central electrode site (Fz; see Figure 6).

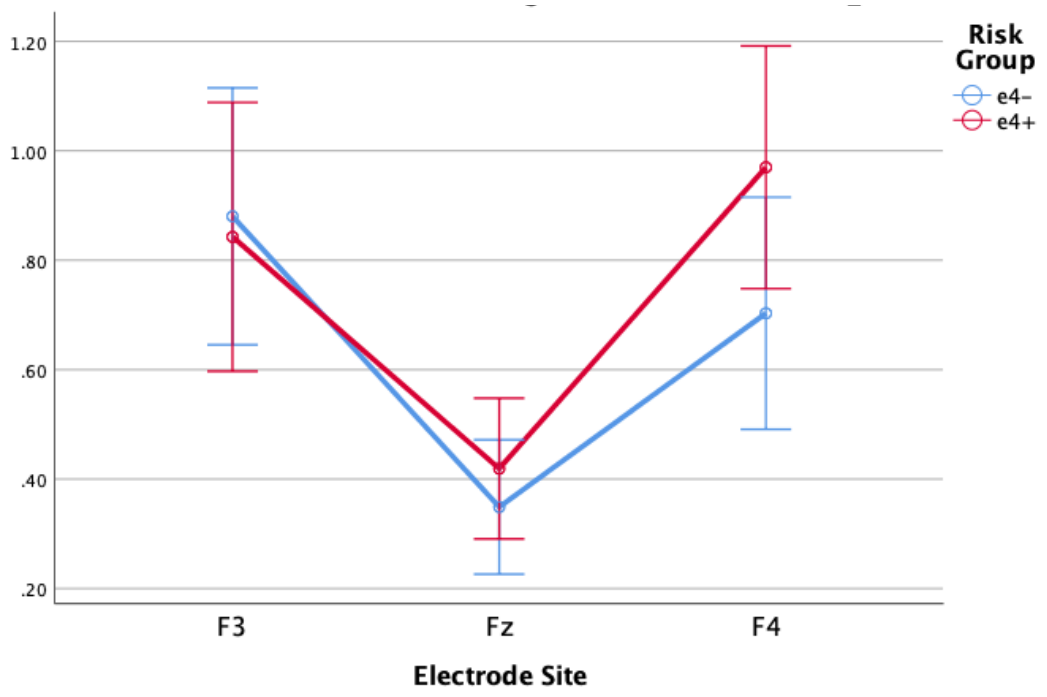

Figure 6. Beta power by risk group (ε4- vs. ε4+) at the F3, Fz, and F4 electrode sites. Beta power is elevated at both left (F3) and right (F4) frontal electrode sites across groups. Beta power at the right frontal electrode site (F4) is slightly elevated in ε4+ individuals when compared to their ε4- counterparts.

An additional post-hoc analysis was performed with younger adults serving as a secondary reference group. A 3x3 mixed ANOVA, with *Group* (APOE ε4+/APOE ε4-/Young Adults) and *Frontal Electrode Site* (F3, Fz, F4) showed a significant *Group* x *Frontal Electrode Site* interaction ($F(4,81) = 3.751$, $p = .006$). Pairwise comparisons revealed greater beta power at Fz for the ε4+ group when compared to the young adult group (p=.006). Furthermore, both ε4+ (p=.001) and ε4- (p<.001) older adults had significantly greater beta power during correct stop trials when compared to the young adult group at the left frontal electrode site (F3). Most notably, the ε4+ older adult group had greater right frontal beta power than the ε4- older adult group (p=.044); the ε4- older adult group also showed greater frontal beta power when compared to the young adults

(p=.018; ε4+ Older Adults > ε4- Older Adults > Young Adults). This pattern of results indicates that the older adults activated both the right and left frontal hemispheres more so than their younger counterparts, while the ε4+ group activated the right hemisphere to a greater degree than their ε4- counterparts (see Figure 7).

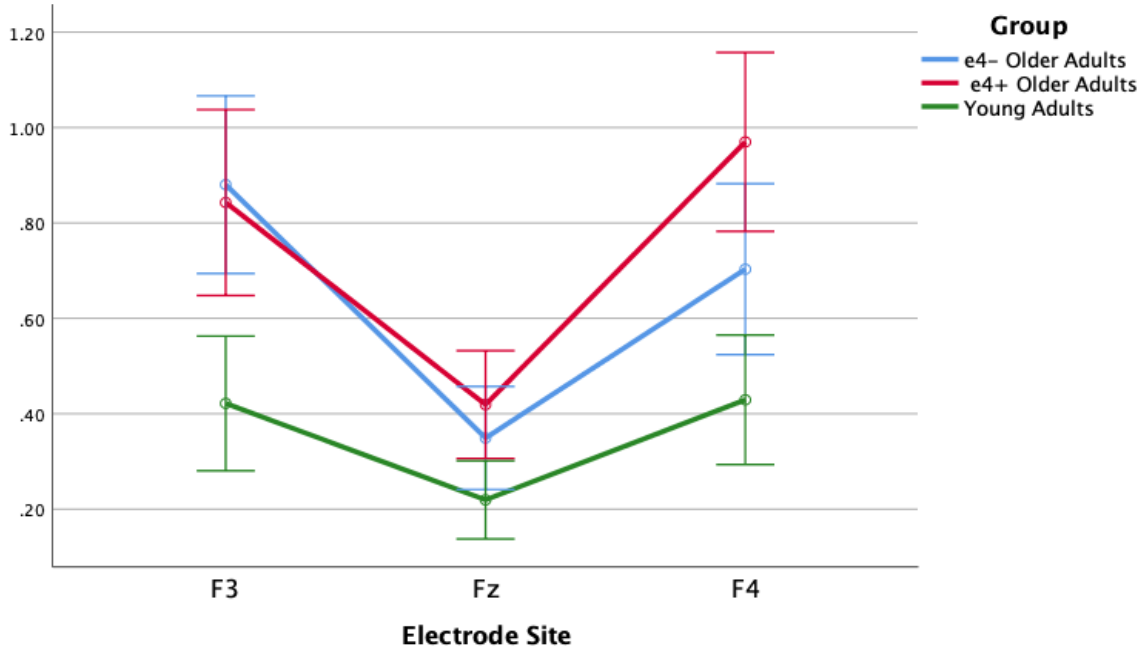

Figure 7. Beta power by age (older adult vs. younger adult) and risk group (ε4- older adults vs. ε4+ older adults) at F3, Fz, and F4 electrode sites. Left (F3) and Right (F4) frontal beta power is elevated across all older adults when compared to their younger adult counterparts. Right frontal beta power (F4) was elevated in ε4+ older adults when compared to ε4- older adults and younger adults (ε4+ > ε4- > younger adults).

Hierarchical Regression Analyses.

In order to explore the degree to which frontal beta power during correct stop trials predicts task performance and traditional neuropsychological tests of executive functioning, hierarchical regression analyses were conducted based on SSRT, SDMT, and TMTB. Demographic variables were included in the model based on significant

exploratory correlations with the outcome variables (i.e., SSRT, SDMT, TMTB), as well as previous literature suggesting that these demographic variables may play a role in performance on these tasks.

Exploratory correlations were performed between demographic variables and cognitive functioning indices. These are presented in Table 3. Age and education were not correlated with SDMT, TMTB, or SSRT. Sex did correlate with SDMT; females had better SDMT performance than males. General cognitive functioning (MMSE) did not significantly correlate with SDMT, TMTB, or SSRT.

In Model 1, age was added in Step 1 and the average of beta power at F3/Fz/F4 electrode site was added in Step 2; SSRT was the outcome variable. In Model 2, age was added in Step 1 and the average of beta power at F3/Fz/F4 electrode site was added in Step 2, with TMTB as the outcome variable. In Model 3, age and sex were added in Step 1 and the average of beta power at F3/Fz/F4 electrode site was added in Step 2; SDMT was the outcome variable.

Results of the hierarchical regression analyses are presented in Table 4. Analyses reveal Model 1 and 2 failed to reach significance when age was entered in Step 1 and when frontal beta power was entered in Step 2. Model 3 reached significance when demographic variables (age and sex) were entered in Step 1, with sex as the significant predictor. The model remained significant at Step 2; however, frontal beta power did not contribute to SDMT prediction.

*Table 3. Exploratory c*orrelations between demographic variables and cognitive indices.

	Sex	Educ	MMSE	SSRT	SDMT	TMTB
Age	.268	-0.058	-0.012	0.064	-0.272	0.271
Sex	--	-0.020	0.026	0.189	-.440*	0.173
Educ	--	--	0.192	0.109	0.254	-0.281
MMSE	--	--	--	-0.031	0.071	-0.125

Note. Educ = Education; MMSE = Mini Mental Status Exam; SSRT = Stop Signal Reaction Time; SDMT = Symbol Digit Modalities Test; TMTB = Trails Making Test Part B.
*Significant correlation at the $p < .01$ level.

Table 4. Results of hierarchical regression analyses with behavioral measures of executive function as the outcome variables.

			Model Summary at Each Step				Contribution of Each Variable at Last Step			
			R^2	ΔR^2	F	p	B	β	t	p
SSRT										
	Step 1		0.064	--	0.168	0.684				
		Age					0.001	0.064	0.41	0.684
	Step 2		0.012	0.008	0.235	0.792				
		Age					0.001	0.063	0.403	0.689
		Frontal Beta					0.009	0.087	0.553	0.584
TMTB										
	Step 1		0.061	--	2.484	0.123				
		Age					1.448	0.248	1.576	0.123
	Step 2		0.093	0.032	1.895	0.165				
		Age					1.511	0.259	1.648	0.108
		Frontal Beta					-13.988	-0.178	-1.135	0.264
SDMT										
	Step 1		0.244	--	6.625	0.003				
		Age					-0.185	-0.107	-0.751	0.457
		Sex					-8.438	-0.45	-3.154	0.003*
	Step 2		0.249	0.005	4.418	0.009				
		Age					-0.179	-0.104	-0.719	0.477
		Sex					-8.626	-0.460	-3.163	0.003*
		Frontal Beta					-1.598	-0.069	-0.497	0.622

Note. *Significant at the $p < .01$ level

Discussion

This study sought to examine the effects of genetic risk for AD on response inhibition using time-frequency analyses of the beta frequency range. While some literature exists demonstrating behavioral and functional differences between cognitively intact carrier and non-carrier elders during executive function tasks (Reinvang et al., 2010; Wishart et al., 2006), less is known regarding response inhibition as a specific executive function of interest within this population (Wetter et al., 2005). This study is the first to examine the relationship between beta power and response inhibition in older adult, cognitively intact ε4 carriers and non-carriers, so as to elucidate the utility of beta band EEG as a prodromal marker of cognitive decline.

Frontal Beta Activity During Go and Stop Conditions

Comparisons of response inhibition-related beta power between correct go and stop conditions demonstrated that beta power was elevated during the correct stop condition compared to the go condition. This elevation in beta power was specifically observed over frontal electrodes when compared to central and parietal electrode sites. These findings support Hypothesis 1, which predicted that beta power at frontal electrodes would be elevated during successful stopping when compared to the go condition in a stop signal task. These findings are generally consistent with the research demonstrating an observed elevation in beta power at frontally place electrodes, particularly over the rIFG (Swann et al., 2009; Wagner et al., 2018) during both successful and failed stop attempts which is absent during correct go trials. These findings in conjunction with our study underscore the implications of beta-band activity in the inhibitory network (i.e., fronto-basal ganglia network; Aron et al., 2014). As such,

the present study adds to the growing body of literature suggesting frontal beta activity may be a specific marker of inhibitory control. Notably, the frontal beta effect was subtle when midline electrode sites were exclusively examined. These initial findings may suggest that beta power during successful stopping is most prominent over the more lateralized frontal electrode sites. As such, a frontal region of interest (ROI) during the stop and go condition better captured stop-related beta activation during a stop signal task.

Frontal Beta Activity in ε4+ and ε4- Risk Groups During Stop

With regard to investigating differences in beta power between genetic risk groups during the stop condition, significant beta power differences were observed at both left and right frontal electrode sites when compared to the fronto-central electrode site. This finding, however, was detected across the older adult sample in both ε4+ and ε4- risk groups. When a young adult reference group was added, results indicated that the ε4+ risk group demonstrated greater frontal beta power at the right frontal electrode site when compared to the ε4- risk group and the younger adult group. Our study also observed greater left frontal beta power during successful stopping in the older adults (across both ε4+ and ε4- risk groups) when compared to their younger counterparts. These findings are in support of Hypothesis 2, in which it was predicted that ε4 carriers would reveal greater frontal beta-band power than non-carriers during successful stopping and are in line with the compensatory theory of aging literature.

While previous research suggests that the frontal beta effect during successful stopping demonstrates right lateralized activity, our results suggest that both older adult

groups demonstrated elevated right and left frontal beta power when compared to their younger counterparts. Compensatory theories of aging indicate that this difference in activation emerges between older and younger adults resulting from neural changes that occur during the aging process (Cabeza, 2002). As such, older adults will recruit additional neural circuitry so as to compensate for the overall decline in neural functioning which can take the form of bilateral recruitment, particularly during tasks that may more typically evoke lateralized activation in younger adults (Cabeza, 2002; Nielson et al., 2002; Reuter-Lorenz & Cappell, 2008). Our findings are also in support of Nielson and colleagues demonstrating that successful inhibition in older adults is accompanied by recruitment in left prefrontal regions as a result of the increase in task difficulty when compared to younger adults (Nielson et al., 2002).

The observed difference specifically in right frontal beta power between the ε4+ group and the ε4-/younger adult groups indicates that individuals at an increased risk for cognitive decline (i.e., ε4+ risk group) may be employing even greater activation than their non-carrier counterparts. While the literature has suggested that successful stopping is accompanied by elevated beta power (Swann et al., 2009), particularly in the rIFG, ε4+ carriers may require even greater activation to successfully inhibit the prepotent response, indexed by greater beta power.

Based on the STAC-r model, experiences throughout the life course can be categorized based on whether they enrich or deplete neural resources (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). For example, variables such as physical fitness, education, and intellectual engagement likely influence enrichment of neural resources, while APOE ε4 likely leads to the depletion of these resources. Thus, the

interaction between life course experiences and the aging process can lead to neural changes at both the structural and functional level resulting in compensatory "scaffolding" (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). Compensatory scaffolding is employed to counteract the depletion of neural resources, and therefore, may be implemented in varying degrees based on the need associated with maintaining cognitive performance. Our findings suggest that older adults, regardless of carrier status, employ compensatory scaffolding in the shape of bilateral neural recruitment. In contrast, due to increased neural depletion elicited by the ε4 allele, carriers of at least one ε4 allele likely must employ additional compensatory mechanisms, such as elevated frontal activation (i.e., elevated right frontal beta power) so as to preserve cognition (Han & Bondi, 2008b; Reuter-Lorenz & Park, 2014).

Notably, carriers of the ε4 allele did not show significantly greater frontal beta-band power during successful stop trials when only midline electrode sites were assessed. It is likely that because the task is right-lateralized, and frontal beta effects are observed particularly at the rIFG, the midline electrodes are not sensitive enough to pick up on the elevated beta-power. As such, it is to be expected that our analyses were more sensitive to the frontal beta effect during successful stopping when lateral electrodes were examined.

Few studies have examined the relationship between beta power and the ε4 allele. Our task-related findings during inhibitory control are generally inconsistent with the few studies that have investigated beta power at rest (Babiloni et al., 2006; Green & Levey, 1999; Lehtovirta et al., 1996; Reinvang et al., 2010). For example, Lehtovirta and colleagues found that ε4 allele carriers with AD demonstrated reduced beta power when

compared to non-carriers (i.e., ε2 or ε3 alleles; Lehtovirta et al., 1996). However, it is likely that AD disease progression in these individuals would have surpassed the neural compensation phase (Han & Bondi, 2008b). In those with MCI, where disease progression is less severe, one EEG rhythm study found no ε4-related differences in beta power, though differences in occipital, temporal, and limbic alpha activity did emerge (Babiloni et al., 2006). Given the existence of cognitive decline in these studies (contrasting with ours), it is likely that the subtle differences we observed in task-related beta power between ε4 carriers and non-carriers would not be observable once cognitive decline is measurable. Our study also demonstrates the utility of examining beta activation specifically during a task assessing inhibitory control, as tasks assessing this specific cognitive process may be more sensitive to the subtle changes in AD progression particularly in at-risk individuals. However, it is also possible that other frequencies, such as alpha, may be more sensitive to ε4 allele-related differences.

Relationship Between Frontal Beta Power and Behavioral Response Inhibition

The results of the present study indicate that frontal beta power did not predict stop signal reaction time (SSRT). This finding is contrary to Hypothesis 3, in which it was predicted that elevated frontal beta power would be positively associated with SSRT, as SSRT may reflect task difficulty. There are several possible explanations for this finding. Firstly, within the context of an older adult sample, it may be that an elevation in frontal beta power during successful stopping is a more sensitive marker of compensation and, therefore, is not evident at the behavioral level (i.e., via SSRT). This explanation is consistent with the compensatory theories of aging and the STAC-r model, which posits that changes in neural structure and function (i.e., scaffolding) precede cognitive changes

(Cabeza, 2002; Reuter-Lorenz & Park, 2014). As such, while SSRT does not differ between risk groups, right frontal beta power did, indicative of neural scaffolding which may help to maintain cognitive performance (i.e., SSRT). Secondly, existing literature suggests a relationship between the specific time of onset in elevated beta power and SSRT (Ray et al., 2012). As a result of the nature of FFT analysis, we were unable to examine this relationship between onset of beta elevation and SSRT. Lastly, it may be possible that elevated frontal beta power is more tightly associated with attentional processes or another cognitive process required during completion of a stop signal task rather than inhibitory control, specifically. Though we believe this to be unlikely, further research is warranted to better differentiate specific cognitive processes related to the elevation of beta power during successful stopping.

Relationship Between Frontal Beta Power and Other Executive Function Processes

Notably, we did not find a relationship between frontal beta power and performance on either TMTB or SDMT. This contrasts with Hypothesis 4, in which it was originally predicted that the role of frontal beta oscillations may extend beyond response inhibition and relate more generally to executive function processes (Babiloni, Babiloni, Carducci, Cappa, et al., 2004; Hwang et al., 2014; Tafuro et al., 2019; Zavala et al., 2017). One explanation is that elevated frontal beta power may be specific to the inhibitory control processes. Miyake and colleagues posit that the three core executive functions (i.e., shifting, updating, and inhibition) are distinct processes with some underlying overlap (Miyake et al., 2000). As such, successful response inhibition may be indexed by frontal beta power, however, other processes (i.e., shifting) may be better characterized by different frequency bands. Moreover, some existing literature has

demonstrated the utility of beta oscillations during working memory tasks (Babiloni, Babiloni, Carducci, Cincotti, et al., 2004). While SDMT does contain a component of working memory, it is likely a better measurement of attention and/or information processing. It may be that tasks more closely related to assessing working memory would better reveal the relationship between frontal beta power and other executive function processes.

Limitations and Future Directions

This study is not without its limitations. The sample size for the present study is relatively small with only 44 cognitively intact older adults and only about half that belong to the APOE ε4+ group. A larger sample would allow for better characterization of differences within and between groups. Additionally, while FFT is commonly used as a method of time-frequency analysis it has some limitations, including the assumption of static frequency during epochs. Though FFT was appropriate given our hypotheses, future research should consider using other time-frequency analyses such as complex Morlet wavelet transforms, which allow examination of temporal and phase components. Future research should also examine other risk factors such as family history and subjective memory complaints. Lastly, future research should explore beta activity during different tasks of executive functioning. While this study only examined task-related beta power during response inhibition (i.e., stop signal task), tasks assessing updating of working memory (updating) and shifting between tasks (shifting) could be differentially sensitive.

Conclusions

The present findings add to the growing literature regarding EEG beta power and inhibitory control by providing additional support for an observable elevation in frontal beta power during successful stopping, which is absent during successful go responses. These findings suggest beta oscillatory activity may be a marker of inhibitory control and are particularly relevant regarding cognitive aging. Our study extended the current research pertaining to task-related beta activity in cognitively impaired elders to a population of *cognitively intact* elders at an increased risk for AD. As such, this study provided evidence that cognitively intact, older adults may employ compensatory neural mechanisms (i.e., bilateral recruitment and greater frontal recruitment) specifically during a task requiring inhibitory control. Additionally, these compensatory mechanisms are even greater in individuals at greater risk for developing AD, consistent with the compensatory "scaffolding" posited in the STAC-r model (Reuter-Lorenz & Park, 2014). This underscores the utility of assessing task-related neural activation during executive function tasks so as to better differentiate individuals at an increased risk for future cognitive impairment. Our study, therefore, demonstrates that EEG oscillatory activity, and more specifically beta band activity, may be a useful prodromal marker of cognitive decline.

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