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Cerebellar EEG source localization reveals age-related compensatory activity moderated by genetic risk for Alzheimer's disease

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Abstract

The Apolipoprotein-E (APOE) ε4 allele is the greatest genetic risk factor for late-onset Alzheimer's disease (AD), but alone it is not sufficiently predictive. Because neuropathological changes associated with AD begin decades before cognitive symptoms, neuroimaging of healthy, cognitively intact ε4 carriers (ε4+) may enable early characterization of patterns associated with risk for future decline. Research in the cerebral cortex highlights a period of compensatory recruitment in elders and ε4+, which serves to maintain cognitive functioning. Yet, AD-related changes may occur even earlier in the cerebellum. Advances in electroencephalography (EEG) source localization now allow effective modelling of cerebellar activity. Importantly, healthy aging and AD are associated with declines in both cerebellar functions and executive functioning (EF). However, it is not known whether cerebellar activity can detect pre-symptomatic AD risk. Thus, the current study analyzed cerebellar EEG source localization during an EF-dependent stop-signal task (i.e., inhibitory control) in healthy, intact older adults (M_{age} = 80 years; 20 ε4+, 25 ε4-). Task performance was comparable between groups. Older age predicted greater activity in left crus II and lobule VIIb during the P300 window (i.e., performance evaluation), consistent with age-related compensation. Age*ε4 moderations specifically showed that compensatory patterns were evident only in ε4-, suggesting that cerebellar compensatory resources may already be depleted in healthy ε4+ elders. Thus, the posterolateral cerebellum is sensitive to AD-related neural deficits in healthy elders. Characterization of these patterns may be essential for the earliest possible detection of AD risk, which would enable critical early intervention prior to symptom onset.

Keywords

cerebellum; event-related potential; source estimation; aging; Apolipoprotein-E; inhibitory control; executive functioning

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CRediT authorship contribution statement

Elizabeth R. Paitel: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Kristy A. Nielson:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Deficits in executive functions may, at least in part, underlie both the mild cognitive declines associated with healthy, normative aging (Deary et al., 2009; Salthouse, Atkinson, & Berish, 2003; Treitz, Heyder, & Daum, 2007; Verhaeghen & Salthouse, 1997) and the severe declines in Alzheimer's disease, including hallmark memory impairment (Alzheimer's Association, 2022; Baudic et al., 2006; Harrington et al., 2013; McKhann et al., 2011; Seo, Kim, Lee, & Choo, 2016). This is because executive functioning represents an umbrella category of higher-order processes that are essential for cognitive control over goal-directed behavior (Miller, 2000; Miyake et al., 2000). These processes may be generally categorized into three groups: set shifting/flexibility, information updating, and inhibitory control (Carlson, Zelazo, & Faja, 2013; Miyake et al., 2000). Inhibitory control, which is the ability to withhold attentional or behavioral responses to irrelevant or interfering stimuli, may be particularly important for global cognitive function. It is also strongly linked to the ability to maintain independent living status, which is a diagnostic criterion for Alzheimer's disease (Amieva, Phillips, Della Sala, & Henry, 2004; Jefferson, Paul, Ozonoff, & Cohen, 2006; Kaiser, Kuhlmann, & Bosnjak, 2018; Munakata et al., 2011; O'Connor & Boyle, 2007; Sweeney, Rosano, Berman, & Luna, 2001).

Because executive functions, including inhibitory control, rely on frontal lobe resources, much research in aging and Alzheimer's disease focuses on those regions (Allain, Etcharry-Bouyx, & Verny, 2013; Binetti et al., 1996; Buckner, 2004; Cabeza, Anderson, Locantore, & McIntosh, 2002; Collette, Van der Linden, & Salmon, 1999; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014; Rodríguez-Aranda & Sundet, 2006; Scharre et al., 2018). However, executive functioning importantly relies on not just frontal lobe function but on effective communication between the frontal lobes and regions of the posterior cerebellum (Bellebaum & Daum, 2007; Schmahmann, 2019; Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012). While less is known about inhibitory control specifically, executive functions in general rely specifically on activity in cerebellar crus I, crus II, and lobule VIIb (Clark, King, & Turner, 2020; Schmahmann, Guell, Stoodley, & Halko, 2019; Stoodley, Desmond, Guell, & Schmahmann, 2021; Stoodley & Schmahmann, 2009; Stoodley et al., 2012). Structural and functional studies show that these regions selectively communicate with areas of the prefrontal, parietal, cingulate, and parahippocampal cortices involved in complex, higher-order cognitive processes (Clark et al., 2020; Jacobs et al., 2018; Schmahmann et al., 2019; Stoodley et al., 2021).

While less investigated than cortical deficits, Alzheimer's disease is associated with deficits in the structure, function, and connectivity of the cerebellum (for review see Hoxha et al., 2018; Jacobs et al., 2018). Consistent with the early presentation of executive dysfunction in Alzheimer's disease, cerebellar deficits begin in the posterior lobe (i.e., cognitive regions) and advance with disease progression to the anterior lobe (i.e., motor regions; Schmahmann et al., 2019; Stoodley et al., 2012). Despite research suggesting that Alzheimer's-related deficits in the cerebellum may occur even earlier than those in the cortex (Bruchhage, Correla, Malloy, Salloway, & Deoni, 2018; Filip, Gallea, Lehéricy, Lungu, & Bareš, 2019; Jacobs et al., 2018; Kuo et al., 2020), research investigating the role of the cerebellum in healthy participants with Alzheimer's risk factors is severely lacking.

In addition to advancing age, inheriting the Apolipoprotein-E (APOE) ε4 allele is the greatest risk factor for late-onset Alzheimer's disease, the predominant form (onset after age 65; Alzheimer's Association, 2022). Specifically, the ε4 allele is associated with up to 12x greater Alzheimer's risk, with an average age of onset about twelve years earlier in ε4 carriers (Alzheimer's Association, 2022; Belloy, Napolioni, & Greicius, 2019; Loy, Schofield, Turner, & Kwok, 2014). While there is variability based on race and geographical location, at least ~25% of the U.S. population carries one or more copies of the ε4 allele (Rajan et al., 2017). Estimates of the lifetime risk associated with carrying an APOE ε4 allele range from ~23–30% in heterozygous ε4 carriers and ~51–60% in homozygous carriers by age 85 (Genin et al., 2011). Thus, despite greater Alzheimer's risk in ε4 carriers (ε4+) relative to non-carriers (ε4-), APOE allelic inheritance alone is not sufficiently predictive of Alzheimer's disease as a stand-alone biomarker (Alzheimer's Association, 2022; Mayeux et al., 1998). Importantly, Alzheimer's-related neuropathological changes may begin decades prior to the onset of cognitive symptoms (Bateman et al., 2012; Jack Jr et al., 2009; Villemagne et al., 2013). Thus, research targeting healthy, cognitively intact ε4+ elders may enable early characterization of neural patterns that are associated with risk for future cognitive decline prior to symptom onset.

While cerebellar research is scarce, a substantial body of research on the cerebral cortex has aimed to characterize age- and ε4-related changes. One product of this work that may also be relevant to the cerebellum is the concept of compensatory recruitment. This refers to a period of increasing brain activation with advancing age that is thought to compensate for age-related neural deficits, enabling maintenance of intact cognitive performance (Cabeza, 2002; Cabeza et al., 2002; Davis et al., 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). The two predominant forms of compensation include greater recruitment of resources from the frontal lobes and the non-dominant hemisphere. Critically, compensatory resources are finite, and as neurological deficits accumulate, brain activation decreases, coinciding with more significant cognitive declines (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). We refer to the exhaustion of these finite compensatory resources as 'depletion' throughout the remainder of the paper. A predominant compensatory model, the Scaffolding Theory of Aging and Cognition-Revised (STAC-r), specifically addresses inheritance of the APOE ε4 allele as a life-course factor that has a substantial impact on neurocognitive processes with aging (Reuter-Lorenz & Park, 2014). Amongst healthy, cognitively intact elders, there is evidence of a period of greater, compensatory activation in ε4+ relative to ε4-, prior to subsequent declines (Han & Bondi, 2008; Han et al., 2007; Rao et al., 2015; Reuter-Lorenz & Park, 2014; Scheller et al., 2018; Sugarman et al., 2012). This early period of compensation may be attributable to early Alzheimer's pathology in ε4+, necessitating recruitment of additional resources earlier than they are needed in ε4- (Belloy et al., 2019; Genin et al., 2011; Reuter-Lorenz & Park, 2014).

Foundational research on compensatory theories of cognitive aging and most of the supporting research to-date uses functional MRI (fMRI) and positron emission tomography (PET). These methods have high spatial resolution but rely on proxy signals for neural activity (e.g., changes in blood oxygenation with fMRI). Moreover, these responses are very slow. Thus, the current understanding of compensatory models reflects activation that is collapsed across periods of at least several seconds, which is much slower than the millisecond-level speed of neural processing in the brain (Hodgkin & Huxley, 1952; Slotnick, 2017). Electroencephalography (EEG), on the other hand, directly captures neural activity on the millisecond scale, ~1,000 times faster than fMRI (Luck, 2014; Slotnick, 2017).

The millisecond-level resolution of EEG has vastly improved understanding of the neural subprocesses that are involved in inhibitory control (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010; Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013; Pires, Leitão, Guerrini, & Simões, 2014). One way of capturing these processes is to ‘lock’ event-related EEG activity to a particular stimulus or response of interest, resulting in event-related potentials (i.e., ERPs; Luck, 2014). The first ERP that reflects inhibitory control is the N200, which is a negative-going wave occurring ~200ms following an inhibitory cue and is generally largest over frontal-central regions. Amplitude is thought to reflect conflict processing (Enriquez-Geppert et al., 2010; Huster et al., 2013; Pires et al., 2014). The second component is the P300, which is a positive-going wave that typically occurs ~300ms post-inhibitory cue. The inhibitory P300 has a generally diffuse pattern of activation, with activation reported in parietal as well as frontal regions. Amplitude is thought to reflect performance monitoring, evaluation, and adaptation/adjustment (Enriquez-Geppert et al., 2010; Huster et al., 2013; Huster, Messel, Thunberg, & Raud, 2020; Pires et al., 2014). Given the well-established role of the cerebellum in predicting, monitoring, evaluating, and updating behavior, the current project focused on P300-related processing in the cerebellum (Bastian, 2006; Blakemore & Sirigu, 2003; Ito, 2008; Sokolov, Miall, & Ivry, 2017; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). This is also consistent with a model from Peterburs and Desmond (2016) suggesting that the cerebellum’s overarching role in cognitive functions is performance monitoring. Specifically, they posit that the cerebellum sends prediction to the prefrontal cortex regarding both whether and when (i.e., temporal prediction) a stimulus will occur. Those expected outcomes are compared with the actual outcomes, which resolve via prefrontal communication back to the cerebellum to evaluate and adjust the next predictions.

Traditionally, cerebellar EEG was not deemed feasible due to its anatomical configuration (i.e., folding patterns) and distance from scalp sensors (Andersen, Jerbi, & Dalal, 2020). A primary limitation to inferring spatial location using scalp-based EEG signals is the concept of volume conduction, which refers to the effects of measuring a signal at a distance from the generator(s) of the source (Baillet, Mosher, & Leahy, 2001; Brunner, Billinger, Seeber, Mullen, & Makeig, 2016; Cohen, 2014). Because multiple brain regions are simultaneously active at any given time, signals that reach each EEG sensor reflect activity from multiple sources (i.e., signal mixing). Additionally, a single underlying source may generate signals that spread to reach multiple sensors at the scalp. Given the electromagnetic superposition principle and the far greater number of sources compared to sensors, finding the inverse solution (i.e., determining the source(s) from the EEG sensor activity) is an ‘ill-posed’ problem, meaning that there is not a unique solution. Many combinations of location, orientation, and magnitude of neural sources could produce the same pattern of activity at the EEG sensors (Cohen, 2014; Grech et al., 2008). Despite this, advancements in source localization (e.g., effective parameters and algorithms for modeling electromagnetic properties of currents in the brain, improved realistic head models), have importantly advanced the opportunity for precise spatial estimation without sacrificing the temporal resolution of EEG (for review see Awan, Saleem, & Kiran, 2019; Kaur, Singh, Bisht, Joshi, & Agrawal, 2022). Indeed, Torres and Beardsley (2019) recently demonstrated that concerns regarding cerebellar imaging with EEG were surmountable with current technology. Using a standard 64-channel EEG array, they were able to clearly isolate task-related motor activity in the cerebellum, which was differentiable, both spatially and temporally, from cortical activity and comparable to what is revealed using fMRI. Furthermore, this study demonstrated that MRI-confirmed, subject-specific anatomical images were not required for accurate cerebellar source localization. Relatedly, Samuelsson and colleagues (2020) quantified the magnitude of cerebellar signals and degree of cancellation, showing that the average cerebellar signals were only ~30% weaker than those from the cortex, with the strongest cerebellar signals generated in posterolateral regions associated with cognitive functioning (i.e., lobule VI, crus I, and crus II). Yet, EEG research modeling cerebellar activity is currently limited by the stark absence of studies with cognitive tasks, despite the advantageous location of relevant cerebellar lobules for EEG detection and analysis (Andersen et al., 2020).

In addition to the data-related advantages of using EEG over other imaging modalities (e.g., excellent temporal specificity, direct recording of population neural firing), there are important practical advantages. Unlike other imaging modalities, there are very few exclusion criteria for EEG, making it a safe and non-invasive option that is available for the vast majority of the population, including people with tattoos, metal below the head (including pacemakers and other medical devices, shrapnel, etc.), anxiety about tight spaces, and people who are pregnant. EEG is also strikingly less expensive than fMRI, the most common alternative. The cost to purchase, install, and maintain an fMRI scanner is exponentially greater than that of purchasing and maintaining EEG equipment. Even beyond this, the costs of scanner time for an fMRI study are estimated to be at least ten times greater than conducting an EEG study (Luck, 2014; Slotnick, 2017). These practical considerations combined with recent advances in EEG source modeling (Andersen et al., 2020; Awan et al., 2019; Kaur et al., 2022; Samuelsson et al., 2020) illustrate the potential for high-impact research that may make it an exceptionally valuable tool for research into early indicators of disease risk.

Thus, the current study aimed to use EEG source localization to characterize both contributions of aging (within a healthy older adult sample) and APOE ε4 on activity in cognitive regions of the cerebellum during the P300 window of successful inhibitory control. First, based on age-related compensatory patterns observed in the cortex (Cabeza, 2002; Cabeza et al., 2002; Davis et al., 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014), we expected older age to predict greater cerebellar activity in regions of the cerebellum involved in executive functions (bilateral crus I, crus II, lobule VIIb). Furthermore, we expected APOE ε4 to moderate the effect of age on cerebellar activity. Specifically, based on evidence of earlier neuropathological deficits in ε4+ (Belloy et al., 2019; Genin et al., 2011; Reuter-Lorenz & Park, 2014) that may begin in the cerebellum even prior to the cortex (Bruchhage et al., 2018; Filip et al., 2019; Jacobs et al., 2018; Kuo et al., 2020), we expected patterns consistent with depletion of age-related compensatory cerebellar resources in ε4+ elders. Thus, we anticipated that in healthy, cognitively intact ε4- elders, older age would predict greater cerebellar activity (i.e., age-related compensation), but that in ε4+ elders, older age would predict lower cerebellar activity (i.e., depleted compensatory resources).

Method

Participants

Healthy, older adult participants (*n* = 49) were recruited from the local community for a larger study and were compensated for their participation. One participant was excluded due to evidence of impaired cognition (ε4+; see Cognitive Screening) and two were excluded due to technical issues during EEG data collection (both ε4+), bringing the sample to 46 participants, including 21 who carried at least one copy of the APOE ε4 allele (ε3/ε4; two subjects had ε4/ε4) and 25 non-carriers (ε3/ε3; three subjects had ε2/ε3). APOE genotype was determined using real-time PCR-based single nucleotide polymorphism analysis; results were not divulged to participants. All procedures were approved by the Marquette University Institutional Review Board and were conducted strictly in line with the ethical approval and the principles of the Declaration of Helsinki.

Measures

Cognitive screening—Participants completed an initial phone screening to assess overall health and potential fit for the study. Upon in-person screening, the Mattis Dementia Rating Scale – Second Edition (DRS-2) was used to screen for intact cognition. A total score of 130/144 was required for study inclusion (Jurica, Leitten, & Mattis, 2001).

Stop-signal task—EEG data were collected during a stop-signal inhibitory control task in which a serial stream of letters was visually presented for 750ms per stimulus with an inter-stimulus interval of 0ms. Participants first completed a Go condition, in which they were instructed to press the space bar for every occurrence of the letter “r” or “s” (504 stimuli, 78 targets). The Go condition serves to establish a prepotent response to those specific stimuli. Afterward, during the Stop-signal condition, participants are instructed to respond to “r” and “s” stimuli (684 stimuli; 81 targets) *unless* the letter is followed by a red flash (i.e., the stop-signal; 36 stop trials), in which case they should withhold their response and wait for the next trial. The stop-signal was presented for a duration of 100ms with variable stop-signal delays at 125ms or 200ms. This approach was selected to ensure high accuracy (≅ 75% vs. 50% with a staircase procedure), while still avoiding predictability (see Elverman, Paitel, Figueroa, McKindles, & Nielson, 2021; Paitel & Nielson, 2021). Behavioral outcome measures include accuracy (go and stop trials) and stop-signal reaction time (SSRT). As successful stop trials are characterized by a non-response, the SSRT is an estimate calculated from the distributions of response time to target trials and the stop-signal delay (Logan, 1994; Logan & Cowan, 1984; Votruba et al., 2008).

EEG Data Acquisition and Preprocessing

EEG data were collected at a 500Hz sampling rate using 64-electrode Brain Products actiCAPs (extended International 10–20 System; ground at AFz; reference at FCz; impedances below 50kΩ), Neuroscan SynAmps, and Neuroscan software (Scan 4.5). A low-pass hardware filter was applied online at 100Hz. EEG data were processed offline using EEGLAB (Version 14.1.0) via MATLAB (Version 7.12, The MathWorks). Upon import, data were visually inspected, and bad electrodes were interpolated as necessary (using spherical splines) to eliminate pervasive channel-level artifacts. The number of channels interpolated was low and comparable between groups ($t(42) = .21$, $p = .84$; $M_{\varepsilon 4-} = .29$ ($SD_{\varepsilon 4-} = .75$; $\text{median}_{\varepsilon 4-} = 0$; $\text{range}_{\varepsilon 4-} = 0–3$); $M_{\varepsilon 4+} = .25$ ($SD_{\varepsilon 4+} = .55$; $\text{median}_{\varepsilon 4+} = 0$; $\text{range}_{\varepsilon 4+} = 0–2$)). Data were re-referenced to a common average and filtered using a zero-phase Hamming-windowed sinc FIR filter to band-pass from 0.5 to 100Hz and a 2nd order Butterworth band-stop (i.e., “notch”) filter from 59–61Hz. An Adaptive Mixture Independent Component Analysis (AMICA; Palmer, Makeig, Kreutz-Delgado, & Rao, 2008) was used to eliminate eye blink artifact. Successful (i.e., correct) trials were then segmented locked to the stop-signal from -100ms pre-stimulus to 800ms post-stimulus, with a 100ms pre-stimulus baseline correction. The segmented data were inspected for any remaining artifact and rejected as needed. A comparable number of trials was included by group ($t(42) = .36$, $p = .72$; $M_{\varepsilon 4-} = 26.79$ ($SD_{\varepsilon 4-} = 3.71$; $\text{median}_{\varepsilon 4-} = 27.50$; $\text{range}_{\varepsilon 4-} = 19–32$); $M_{\varepsilon 4+} = 26.30$ ($SD_{\varepsilon 4+} = 5.28$; $\text{median}_{\varepsilon 4+} = 27.00$; $\text{range}_{\varepsilon 4+} = 17–34$)). Unaveraged, single trial data for successful stop-signal trials were exported to open-source Brainstorm software (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011) for further analysis.

Source analysis

Data processing steps for source estimation are displayed in Figure 1. Volume head models were constructed via OpenMEEG (Gramfort, Papadopoulo, Olivi, & Clerc, 2010; Gramfort, Papadopoulo, Olivi, & Clerc, 2011) using an adaptive integration approach in which the sampling of grid points is denser at the surface (nearer the EEG sensors; started at 4,000 grid points). Each subsequent layer (moving inward toward the center of the brain) was down-sampled by a factor of three, which was repeated 17 times or until there were no remaining vertices. This approach resulted in models with 15,979 grid points. These realistic head models account for three realistic layers (i.e., scalp, inner skull, and outer skull) as well as variability in the conductivity of different head tissues (relative conductivity values: scalp = 1; outer skull = .0125; inner skull = 1). Because EEG signals measured at the scalp are generated within the brain and must be transmitted through the various head tissues, these realistic models are superior to simple, traditional models that use three spheres and fit the outer sphere to the electrode positions (Michel & Brunet, 2019; Michel & Murray, 2012; Tadel et al., 2019).

The electromagnetic properties of the head tissues and scalp electrodes are then used to estimate the sources of the EEG signals measured at the scalp. Based on the expectation that sources for these data would be distributed (vs. focal activation common to earlier, more sensory-perceptual event-related EEG activity), a depth-weighted minimum norm imaging approach was applied (Hämäläinen & Ilmoniemi, 1994; Lin et al., 2006; Mahjoory et al., 2017; Tadel, Bock, Mosher, Leahy, & Baillet, 2021). The noise and data covariance matrices were computed using each participant’s single trial data, with -100 to 0ms for noise covariance and 0 to 700ms for data covariance. Given the use of volume source space, dipole orientation was unconstrained, resulting in three orthogonal dipoles at each grid point. Resulting source maps were z-score normalized relative to the pre-stimulus baseline period to increase the signal-to-noise ratio and create consistent metrics across participants.

Given the unconstrained sources, each grid point had three time series (one for each dipole orientation (x, y, z)). The maximum value in each dipole was found, and the norm of the three orientations was computed (sqrt $\max(x^2) + \max(y^2) + \max(z^2)$), resulting in one value per grid point for every time point. These normed values were used to obtain an absolute (vs. relative) value, based on interest in magnitude of activation regardless of polarity (Tadel et al., 2019). The maximum norm value within each region of interest (ROI) was then extracted for each time point. Based on previous research with older adults (e.g., Elverman et al., 2021; Paitel & Nielson, 2021) and visualization of time series data (see Supplementary Figure 1), max activation within each ROI was then averaged across 330–550ms to target P300-related activity. This window is consistent with relatively delayed P300-related processes in older (vs. young) adults (Cheng, Tsai, & Cheng, 2019; Elverman et al., 2021; Patel & Azzam, 2005). Cerebellar ROIs were selected *a priori* based on regions involved in executive functions (Clark et al., 2020; Mannarelli et al., 2020; Stoodley et al., 2021; Stoodley & Schmahmann, 2009; Stoodley et al., 2012) and sensitive to early Alzheimer's disease (Gellersen, Guell, & Sami, 2021; Guo et al., 2016). These regions were isolated using the AAL3 atlas (Rolls, Huang, Lin, Feng, & Joliot, 2020): bilateral crus I, crus II, and lobule VIIb.

Procedure

EEG data during the stop-signal task were collected as part of a larger study. Participants completed individual testing sessions, and informed consent was completed at the beginning of the session. During EEG data collection, participants were seated in front of a computer and instructed to limit gross motor movements and speech to minimize noise in the EEG data. Stop-signal task instructions were read aloud as they appeared on the screen. Participants were given the opportunity to ask questions and feedback was provided during a practice block. No feedback was provided during task performance.

Statistical approach

Multiple moderation models were structured with Age predicting cerebellar Source activity in bilateral crus I, crus II, and lobule VIIb. APOE ε4 was added as a moderator (PROCESS model 1 – simple moderation; Hayes, 2022). This model structure allows for the investigation of Age*APOE interaction terms in which the effect of Age on Source is dependent on APOE ε4 group. Cerebellar regions were investigated bilaterally due to evidence of involvement of both hemispheres in cognitive functions (Schmahmann et al., 2019; Stoodley et al., 2021; Stoodley & Schmahmann, 2009; Stoodley et al., 2012) and substantial evidence of bilaterality with older age (Bernard & Seidler, 2012; Cabeza, 2002; Carp, Park, Hebrank, Park, & Polk, 2011; Naccarato et al., 2006; Reuter-Lorenz & Park, 2014).

Results

Descriptive statistics and excluded data

One participant (ε4+) had extreme source values suggestive of poor data quality. This participant was excluded from analyses, resulting in a final sample of 45 participants, including 20 ε4+ and 25 ε4-. Sample demographics are presented in Table 1 by APOE ε4 group. Independent samples *t*-tests were used to compare all demographics, with the exception of sex distribution, which was assessed using a $\boldsymbol{X}^2$ test. The groups were comparable in age, sex distribution, and DRS scores. The ε4+ group had on average 1.5 years more education than the ε4- group, which was statistically significant. However, it should be noted that greater education in ε4+ is considered a protective factor. This would therefore be expected to *reduce* rather than increase group differences. Nevertheless, education was added as a covariate in the moderation analyses.

Task performance

Performance on the stop-signal task is presented by APOE ε4 group in Table 2. Performance was compared using independent samples *t*-tests. Groups did not significantly differ on any task metrics, including percent correct inhibitory trials (PCIT; stop-signal trials), percent correct target trials (PCTT; go target trials), or SSRT.

Source analysis results

Education was not a significant covariate in any of the moderation models (see Table 3). While sex did not significantly differ by ε4 group (see Table 1), because the distribution was not equal, we verified that sex did not significantly correlate with the cerebellar source (i.e., outcome) variables. Cerebellar source models were significant with left crus II and left lobule VIIb. In both, age was a significant predictor of cerebellar activity, such that within this older adult sample, older age predicted greater activity (see Figures 2 & 3; Table 3). This relationship was moderated by APOE ε4 in both left crus II and left lobule VIIb, with older age predicting greater activity only in the ε4- group. The ε4+ group did not show this greater activity with older age. Follow-up contrasts comparing ε4 groups clarified that ε4- had trending patterns of greater activation than ε4+ only in the oldest participants (*p*s = .06; see Table 3).

Discussion

The current study used EEG source localization to examine the impact of older age and APOE ε4 inheritance on cerebellar activity during successful inhibitory control in the P300 window. In this sample of healthy, cognitively intact older adults, older age predicted greater cerebellar activity during successful inhibition in left crus II and left lobule VIIb. Furthermore, the interaction of age and APOE ε4 was significant in both regions, clarifying that older age predicted greater activity specifically within the ε4- group. ε4+ deviated from this pattern and did not show greater cerebellar activity with older age.

Compensatory cerebellar activity

The findings in this study, using an older sample in which there was high and comparable task accuracy across the genetic groups, suggest that increased cerebellar activation with age serves a compensatory role, but this compensatory capacity may already be depleted in healthy ε4+ of the same age (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). Specifically, as age-related neural deficiencies accumulate in ε4-, greater cerebellar activation likely contributes to maintenance of intact task performance. In contrast, neural degradation is thought to begin at an earlier age in ε4+ (Belloy et al., 2019; Genin et al., 2011; Reuter-Lorenz & Park, 2014), possibly even earlier in cerebellum than in the cortex (Bruchhage et al., 2018; Filip et al., 2019; Jacobs et al., 2018; Kuo et al., 2020), which would invoke and then deplete compensatory reserves at an earlier age. This interpretation fits the current findings in this older sample (mean age = 80 years), where contrasts showed that cerebellar activity was lower in the oldest ε4+ compared with ε4-. While the groups did not significantly differ at the younger end of this age span, there appears to be modestly greater activity in the ε4+ group in these regions, which we hypothesize would be more robust with larger samples.

The current cerebellar EEG findings support and expand upon a longitudinal study that used a high-accuracy semantic memory task to evaluate age-related patterns in cortical fMRI activation by APOE ε4 (Rao et al., 2015). At baseline, healthy, cognitively intact older ε4+ had greater activation than comparable ε4-. Over the five-year follow-up period, activation in ε4- increased, consistent with expected age-related compensation, while activation in ε4+ decreased over the same period, coincident with episodic memory decline and hippocampal atrophy. The current results from a cross-sectional study fit very well with this framework and expand it to include the under-studied role of the cerebellum during inhibitory performance evaluation. We provide the following figure to illustrate theoretical trajectories of age-related compensatory activation, separated by APOE ε4 group (see Figure 4).

Despite the consistency of our data with depleted compensatory resources in ε4+, there was no evidence of poorer performance in ε4+ during the stop-signal task. There are likely two principal explanations. First, while the stop-signal inhibitory control task assesses complex cognitive functions, it is designed to be relatively low-demand and high-accuracy (Elverman et al., 2021; Paitel & Nielson, 2021). Even compared to other inhibitory control tasks, such as go/no-go paradigms, the stop-signal task is less dependent on working memory, creating lower demand and allowing for more comparable task performance between ε4 groups (Cheng et al., 2019; Paitel & Nielson, 2021; Rubia et al., 2001). This comparable and high-accuracy task performance is critical for interpreting differences in neural activation in the context of compensatory theories of aging (Reuter-Lorenz & Cappell, 2008). Behavioral performance differences between groups introduce confounds to neural activation that are attributable to task difficulty and error networks. That being said, assessment of higher-demand cognitive processes would be more, rather than less, likely to reveal deficits in the ε4+ elders. Indeed, the longitudinal fMRI study from Rao and colleagues (2015) analyzed brain activation during a high-accuracy semantic memory task and showed cognitive deficits over time in ε4+ not within that lower-demand task, but rather in episodic memory, which is higher-demand (Reuter-Lorenz & Cappell, 2008). Second, the current sample consists of highly educated older adults who met screening criteria for intact cognitive functioning despite their older age and genetic risk. Thus, the current study preferentially captures those who have maintained high cognitive performance despite the neural consequences of age and ε4. Greater educational attainment may also have minimized impending performance deficits (Chapko, McCormack, Black, Staff, & Murray, 2018; Roldán-Tapia, Cánovas, León, & García-Garcia, 2017; Stern, 2002). A larger sample with a greater range in education and cognitive functioning would more likely reveal deficits in the oldest ε4+ participants.

Cognitive cerebellar ROIs

The role of the posterior cerebellum, particularly crus I/II and lobule VIIb, during successful inhibitory control in the present study expands upon existing research linking activation in these regions with executive functions (King, Hernandez-Castillo, Poldrack, Ivry, & Diedrichsen, 2019; Stoodley & Schmahmann, 2009). Functional mapping from King et al. (2019) highlighted the role of bilateral crus I and II in active maintenance of information, divided attention, and interference resolution. They showed the role of lobule VIIb specifically in attention networks and motor planning (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; King et al., 2019). Relatedly, a meta-analysis of fMRI and PET studies contrasted activation during various executive tasks (e.g., go/no-go, Tower of London, decision-making, random number generation) vs. tasks assessing spatial, verbal, working memory, and affective functions. Activity during executive functions was isolated to left crus I and lobule VIIb (Stoodley & Schmahmann, 2009). The results were generalized across executive tasks, pointing to a potentially important role of left crus I and lobule VIIb in the overall cognitive control that is relevant to most executive tasks (e.g., Niendam et al., 2012). The current findings expand upon these previous studies to suggest specific involvement of crus II and lobule VIIb in inhibitory performance evaluation within a sample of healthy older adults (Enriquez-Geppert et al., 2010; Huster et al., 2013; Huster et al., 2020).

Some previous research has suggested a relative vulnerability of crus I and II to age- and Alzheimer's-related risk. Specifically, both healthy aging and Alzheimer's disease have been associated with grey matter loss selectively in crus I and crus II (Abe et al., 2008; Alexander et al., 2006; Gellersen et al., 2021; Guo et al., 2016). Studies of resting state intrinsic connectivity and transcranial magnetic stimulation (TMS) have shown that bilateral crus I and II are functionally connected with regions of the cortex involved in the default mode network (Bernard & Seidler, 2014; Buckner et al., 2011; Guo et al., 2016; Halko, Farzan, Eldaief, Schmahmann, & Pascual-Leone, 2014), which is one of the earliest networks impacted by Alzheimer's-related neuropathology (Greicius, Srivastava, Reiss, & Menon, 2004; Mevel, Chételat, Eustache, & Desgranges, 2011; Simic, Babic, Borovecki, & Hof, 2014). The current findings suggest that functional, task-related activity in left crus II and lobule VIIb may reveal early age- and ε4-related vulnerabilities, even before symptom onset. Research with Alzheimer's groups largely relies on resting state analysis, which preferentially activates regions in the default mode network (e.g., crus I/II), rather than those associated with networks that are more active during task engagement. Connectivity studies with healthy samples show that lobule VIIb plays an important role in frontal-parietal attention networks, which are preferentially active during task engagement, with greater activation during higher task demand (Brissenden & Somers, 2019; Buckner et al., 2011; Chen & Desmond, 2005; Habas, 2021; King et al., 2019). Specifically, a strong case has been made for the role of lobule VIIb in the dorsal attention network, which is involved in top-down, goal-directed attention toward task-relevant stimuli (Brissenden, Levin, Osher, Halko, & Somers, 2016; Brissenden & Somers, 2019; Brissenden et al., 2018). Thus, tasks such as the stop-signal that assess complex cognitive processes while allowing for high-level task performance may be important for capturing age- and Alzheimer's risk-related neural effects, particularly in regions outside of the default mode network.

The current results demonstrated age by APOE ε4 interactions that were significant specifically in the left cerebellar hemisphere. Research on cerebellar lateralization during cognitive tasks in young participants generally points to a right hemisphere dominance for language tasks, left hemisphere dominance for visual-spatial tasks, and bilateral activation during executive functions (Schmahmann et al., 2019; Stoodley et al., 2021; Stoodley & Schmahmann, 2009; Stoodley et al., 2012). The impact of age on cerebellar lateralization is less clear, with some evidence of increased bilaterality in older age during resting state (Bernard & Seidler, 2012) and in motor tasks (Carp et al., 2011; Naccarato et al., 2006). Greater bilaterality with age is consistent with age-related compensatory patterns evident in the cerebral cortex (Cabeza, 2002; Reuter-Lorenz & Park, 2014).

Because the current models specifically assess the impact of age and Alzheimer's risk, it is notable that there is some evidence of a right cerebellar hemisphere vulnerability in Alzheimer's disease (Gellersen et al., 2021). A recent meta-analysis isolated a pattern of right lateralized grey matter loss in crus I and II that differentiated Alzheimer's disease from healthy aging, which evidenced bilateral patterns of grey matter loss (Gellersen et al., 2021). Yet, a similar study reported significant cerebellar atrophy in Alzheimer's disease relative to age-matched healthy controls in bilateral crus I and crus II (Guo et al., 2016). Furthermore, some work in those with mild cognitive impairment (MCI), which is often considered a transitional stage to Alzheimer's disease, has pointed to left-lateralized cerebellar effects during resting state (Bai et al., 2011). Taken together, the literature is currently mixed regarding potential lateralized Alzheimer's-related vulnerability in the cerebellum.

During the P300 window during successful inhibitory control, our findings point to age-related compensatory recruitment in left crus II and lobule VIIb in healthy, cognitively intact ε4- elders, while this compensation capacity may be depleted in ε4+. There are two potential explanations for these left-lateralized patterns. First, inhibitory P300 activity in the cerebral cortex tends to be right-hemisphere dominant (Enriquez-Geppert et al., 2010; Huster et al., 2013; Huster et al., 2020; Paitel & Nielson, 2021). Given the predominately contralateral projections between the cerebellum and cortex (Bostan, Dum, & Strick, 2013; Krienen & Buckner, 2009), the left-lateralized effects may reflect relatively greater demand on these specific networks (right cortical ⟷ left cerebellar) during successful inhibitory performance evaluation. It is also possible, however, that this approach is capturing hemisphere-specific cerebellar vulnerabilities that may precede those evidenced in MCI and Alzheimer's disease (Bai et al., 2011; Gellersen et al., 2021; Guo et al., 2016; Hoxha et al., 2018; Jacobs et al., 2018). Specifically, greater activity in left crus II and lobule VIIb with older age in healthy ε4- may suggest that those regions are more vulnerable to age-related neural deficits, thus necessitating greater magnitude of activation to maintain high task performance (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014).

Limitations and future directions

Future research capturing younger stages of older adulthood and incorporating middle-age participants may be key for detecting the earliest possible signs of risk for Alzheimer’s disease-related pathology. The current results with an older sample, older than is typical in many cognitive aging studies, suggested that compensatory cerebellar resources may be depleted in ε4+ participants. Thus, looking earlier might increase the likelihood of detecting the earlier compensatory phase of activation in ε4+ (see Figure 4). This approach may be fundamentally important for early detection and intervention in those with elevated risk for Alzheimer’s disease.

While the gene groups in the current study did not significantly differ in sex distribution, there was a greater percentage of women in the ε4+ group (i.e., 16 female/4 male ε4+, 17 female/8 male ε4-). A balanced sex distribution would be statistically advantageous. However, there is evidence of greater Alzheimer’s risk in women, beyond what is attributable to longevity (Alzheimer’s Association, 2022; Riedel, Thompson, & Brinton, 2016), and a greater influence of ε4+ on women (Altmann, Tian, Henderson, Greicius, & Investigators, 2014; Rahman et al., 2020). As such, future research directly interrogating the influence of sex in these patterns may provide important insights.

The current analyses investigated cerebellar activity during the P300 time window, corresponding with inhibitory performance monitoring, evaluating, and updating (Enriquez-Geppert et al., 2010; Huster et al., 2013; Huster et al., 2020), in line with well-established cerebellar prediction and updating processes (Bastian, 2006; Blakemore & Sirigu, 2003; Ito, 2008; Peterburs & Desmond, 2016; Sokolov et al., 2017; Tseng et al., 2007). There may also be important cerebellar contributions during the inhibitory N200 window, corresponding with conflict processes (Clark et al., 2020; Mannarelli et al., 2020). The impact of age and Alzheimer’s risk on these inhibitory subprocesses may be an important focus of future research.

It is well-established that cognitive regions of the cerebellum communicate in feed-back and feed-forward loops with regions of the cortex involved in higher-order cognitive processes, including prefrontal and association cortices (Schmahmann et al., 2019; Stoodley et al., 2012). Thus, given the feasibility of cerebellar source estimation, EEG source-level functional connectivity assessing frontal-cerebellar connectivity during executive functions is a necessary next step for understanding network-level activation patterns. Additionally, some research points to stronger results using functional connectivity relative to activation within the cerebellum in MCI and early stages of Alzheimer’s disease (Bai et al., 2011; Hoxha et al., 2018; Jacobs et al., 2018; Jernigan et al., 2001; Pagen et al., 2020). Thus, functional connectivity may prove a particularly robust approach for detecting and predicting early patterns associated with Alzheimer’s risk.

Conclusions

The current results demonstrate the feasibility of cerebellar EEG source localization during a complex but high-accuracy inhibitory control task. We further provide evidence for age-related compensatory cerebellar activity during the P300 window in healthy, cognitively intact ε4- elders. Specifically, greater activity in left crus II and left lobule VIIb may be important for maintaining sufficient inhibitory performance monitoring processes to support intact inhibitory control with older age. However, patterns in this relatively old ε4+ sample (mean age = 80 years) were consistent with depletion of cerebellar resources, suggesting that the posterolateral cerebellum may be impacted early in healthy elders with genetic risk for Alzheimer’s disease.

The current findings and methodology aim to provide an important launch point for furthering understanding of the impact of aging and neuropathology on the cognitive cerebellum. While our interests lie in Alzheimer’s disease, cerebellar dysfunction is implicated in a vast number of neurological and psychopathological conditions, including Parkinson’s disease, Huntington’s disease, autism spectrum disorder, psychotic disorders (including schizophrenia), depression, and anxiety disorders (Becker & Stoodley, 2013; Franklin, Camargo, Meira, Lima, & Teive, 2021; Heslin, Shaffer, Powers, Andreasen, & Parker, 2020; Minichino et al., 2014; Moreno-Rius, 2018; Wu & Hallett, 2013). As such, the methodological approach presented in this study could potentially be extended and applied to a wide range of neurological disorders beyond Alzheimer’s disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The de-identified data presented in this study are available on request to the corresponding author (KAN).

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Impact statement:

This study details the first application of EEG cerebellar source localization to aging and genetic risk for Alzheimer’s disease (AD). The results demonstrate age-related compensatory recruitment in cognitive regions of the cerebellum during inhibitory control, which may be already depleted in healthy, cognitively intact elders with genetic risk for AD.

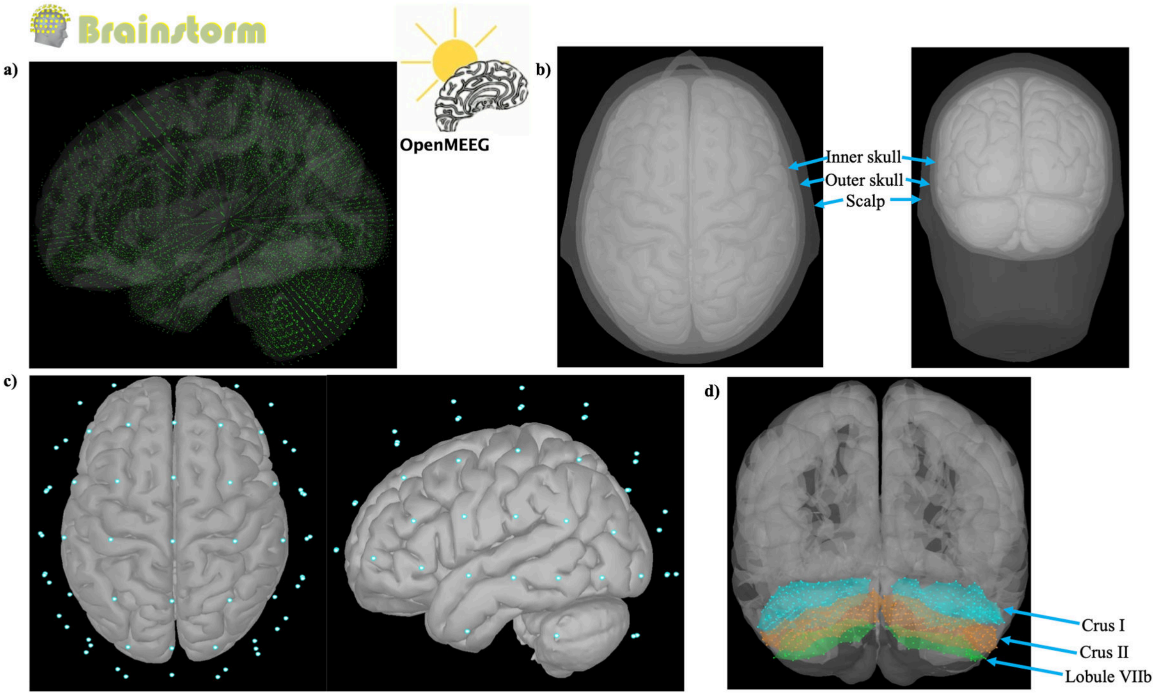
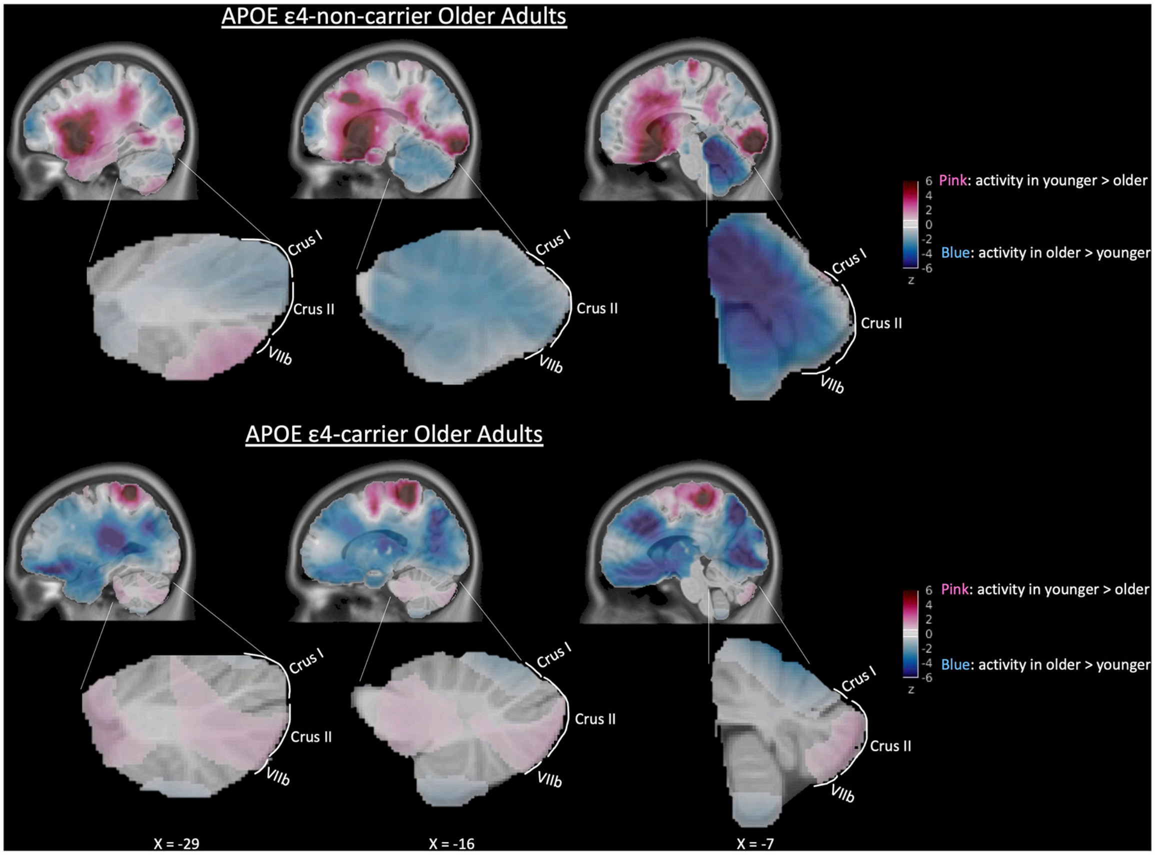


Figure 1.

Data processing steps for source localization. a) Adaptive integration volume model (total 15,979 grid points; via OpenMEEG (Gramfort et al., 2010)); b) Three layers of realistic head models: inner skull, outer skull, and scalp; c) Model EEG sensor locations (represented by white/teal dots); d) AAL3 atlas showing cerebellar regions of interest (Rolls et al., 2020).



APOE ε4-non-carrier Older Adults

APOE ε4-carrier Older Adults

Figure 2.

Cerebellar source activity by APOE ε4 group in left hemisphere sagittal sections (section shown = X coordinate); ROI outlines based on coordinates from AAL3 atlas (Rolls et al., 2020; Schmahmann et al., 1999). Maps show z-score activity increase from pre-stimulus baseline period, averaged over the P300 window (330 to 550ms in this older sample). ε4 groups are contrasted by age percentiles, with greater activity in younger age (age < 33.33rd percentile; 72–77 years) shown in **pink** and greater activity in older age (age > 66.66th percentile; 82–89 years) in **blue**. Within ε4-, cerebellar activity was overall greater in older participants. ε4+ showed patterns of greater activity in the younger participants, though these were not statistically significant (see Table 3).

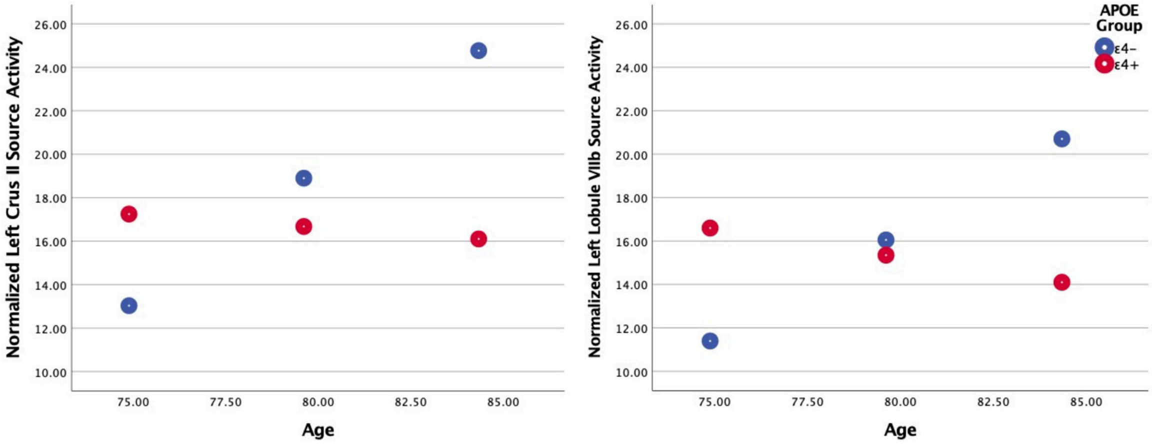


Figure 3.

Moderation analysis plots showing the significant Age*APOE interactions, with cerebellar source activity (z-score normalized relative to the pre-stimulus baseline period) plotted by gene group at age points -1*SD* (74.79 years), mean (79.52 years), and +1*SD* (84.25 years) with education covaried (i.e., simple-slopes analysis, via PROCESS (Hayes, 2022)). Older age predicted greater cerebellar activity, which was significant only in ε4- (**blue** dots). ε4+ (**red** dots) did not show greater activity with older age. ε4- had trending patterns of greater cerebellar activity than ε4+, only in the oldest participants. The findings suggest that age-related cerebellar compensatory capacity may have already been depleted in ε4+.

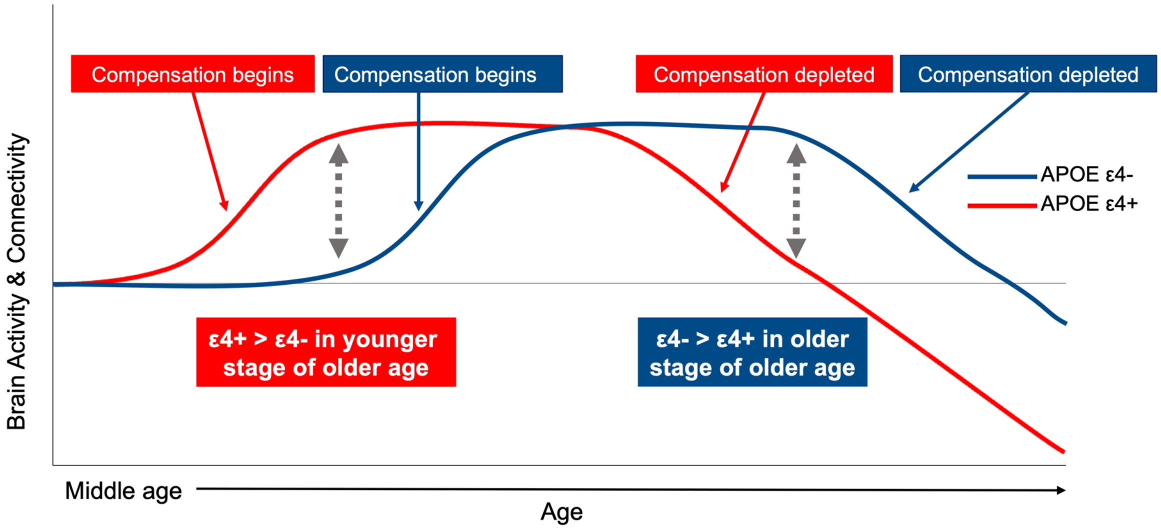


Figure 4.

A theoretical model of differing neural aging trajectories in middle age to older adulthood by APOE ε4. Due to earlier neural deficits, compensatory resources are recruited earlier in ε4+ (**red** line) vs. ε4- (**blue** line). Because ε4+ recruit these resources earlier, there is a period in the younger stage of older age where brain activity and connectivity are greater in ε4+ vs. ε4-. Just as compensatory resources are recruited earlier in ε4+, they are also depleted earlier. These earlier decreases in brain activity/connectivity then result in greater activity in ε4- vs. ε4+ during the older stage of older age. Thus, by targeting healthy ε4 carriers during early stages of older adulthood, neuroimaging research may capture early stages of compensatory brain activation in ε4+, which may be indicative of risk for future decline. As this theoretical model is intended to guide hypotheses for future research, it should be noted that the actual trajectories of brain activity and connectivity patterns are expected to vary by sample characteristics and ‘reserve’ or resilience factors (e.g., sex, education, health, fitness, etc.), and by brain region(s), context(s) (e.g., task type, resting state), and temporal component(s) of interest.

Table 1.

Demographics by APOE ε4 group (mean(SD))

	APOE ε4+ (*n*=20)	**APOE ε4− (*n*=25)**	***t*(*p*)^**
Age	78.90 (4.54)	80.19 (4.89)	.906(.370)
Education	**15.70 (2.43)**	**13.96 (1.84)**	**−2.737(.009)**
Sex (%female)	80.00%	68.00%	.818(.366)
DRS	137.90 (3.39)	138.88 (2.89)	1.047 (.301)

Note.

^for sex comparison, the statistic is $X2$; bold: $p < .05$.

Table 2.

Stop-signal task performance metrics by APOE ε4 group (mean(SD))

	APOE ε4+ (*n*=20)	**APOE ε4− (*n*=25)**	***t*(*p*)**
Stop-signal reaction time (SSRT; ms)	548.23 (27.21)	539.87 (39.34)	−0.807 (0.424)
% correct inhibitory trials (PCIT)	72.92 (14.53)	76.11 (9.28)	0.896 (0.375)
% correct target trials (PCTT)	98.21 (3.70)	98.86 (1.38)	0.818 (0.418)

Table 3.

Cerebellar source analysis moderation models

	R^2	**MSE**	***F***	***p***		**R^2**	**MSE**	***F***	***p***
L crus I	0.165	91.473	1.9683	0.118	**R crus I**	0.019	150.384	0.659	0.624
	coeff	***SE***	***t***	***p***		**coeff**	***SE***	***t***	***p***
Age	**0.809**	**0.406**	**1.992**	**0.053**	**Age**	0.673	0.521	1.292	0.204
APOE	72.956	51.422	1.419	0.164	**APOE**	29.966	65.933	0.455	0.652
Age*APOE	−0.934	0.643	−1.453	0.154	**Age*APOE**	−0.401	0.824	−0.486	0.630
Education	−1.249	0.707	−1.767	0.085	**Education**	0.4987	0.906	0.550	0.585
	R^2	**MSE**	***F***	***p***		**R^2**	**MSE**	***F***	***p***
L crus II	**0.237**	**98.080**	**3.098**	**0.026**	**R crus II**	0.108	141.395	1.208	0.323
	coeff	***SE***	***t***	***p***		**coeff**	***SE***	***t***	***p***
Age	**1.241**	**0.421**	**2.951**	**0.005**	**Age**	*0.939*	*0.505*	*1.861*	*0.070*
APOE	**106.199**	**53.247**	**1.995**	**0.053**	**APOE**	68.108	63.932	1.065	0.293
Age*APOE	**−1.362**	**0.666**	**−2.046**	**0.047**	**Age*APOE**	−0.896	0.799	−1.122	0.269
Education	−1.132	0.732	−1.547	0.130	**Education**	0.325	0.879	0.396	0.694
Follow-up contrasts									
	effect	***SE***	***t***	***p***					
ε4-	**1.241**	**0.421**	**2.951**	**0.005**					
ε4+	−0.1209	0.5052	−0.239	0.900					
Age -1*SD*	4.217	4.640	0.909	0.369					
Age mean	−2.224	3.258	−0.683	0.499					
Age +1*SD*	*−8.665*	*4.419*	*−1.961*	*0.057*					
	R^2	**MSE**	***F***	***p***		**R^2**	**MSE**	***F***	***p***
L VIIb	**0.224**	**59.121**	**2.878**	**0.035**	**R VIIb**	0.120	140.387	1.363	0.264
	coeff	***SE***	***t***	***p***		**coeff**	***SE***	***t***	***p***
Age	**0.984**	**0.327**	**3.014**	**0.005**	**Age**	**1.008**	**0.503**	**2.004**	**0.052**
APOE	**98.668**	**41.340**	**2.387**	**0.022**	**APOE**	90.269	63.704	1.417	0.164
Age*APOE	**−1.248**	**0.517**	**−2.415**	**0.020**	**Age*APOE**	−1.171	0.796	−1.470	0.149
Education	−0.861	0.568	−1.516	0.137	**Education**	0.433	0.876	0.494	0.624
Follow-up contrasts									
	effect	***SE***	***t***	***p***					
ε4-	**0.984**	**0.327**	**3.014**	**0.005**					
ε4+	−0.264	0.3923	−0.673	0.505					
Age -1*SD*	5.202	3.602	1.444	0.157					
Age mean	−0.701	2.530	−0.277	0.778					
Age +1*SD*	*−6.604*	*3.431*	*−1.925*	*0.061*					

Note. coeff = coefficient; **Bold**: $p < .05$; *italics*: $p = .055\text{-}.080$.