Aging, Executive Function, Fronto-Parietal Network Cortical Thickness: Insights from Cognitive Reserve

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AGING, EXECUTIVE FUNCTION, FRONTO-PARIETAL NETWORK CORTICAL THICKNESS: INSIGHTS FROM COGNITIVE RESERVE

by

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ABSTRACT
AGING, EXECUTIVE FUNCTION, FRONTO-PARIETAL NETWORK CORTICAL THICKNESS: INSIGHTS FROM COGNITIVE RESERVE

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Cognitive reserve (CR) indexes the nonlinear relationship between neurological insult and behavioral change. CR is manifested in both static factors (e.g., childhood environment, education) and modifiable lifestyle factors, (e.g., leisure activities). Detailed investigation of the influence of CR on cortical thickness, which indexes neuropathology, and cognitive functioning could be particularly important in understanding the heterogeneity of Alzheimer's disease (AD). While memory decline is the hallmark of AD, executive functioning (EF) decline often predates memory changes, making EF an important target for investigating CR influences.

The current study examines the relationship of CR and genetic risk for AD (ε4) on EF as it relates to fronto-parietal neural network cortical thickness, and memory performance as it relates to medial temporal lobe thickness and hippocampal volume. This study addresses the heterogeneity of CR measurement by examining three different CR factors (CR1=IQ; CR2=IQ, Activities, CR3=IQ, Activities, Health) in 35 healthy elders age 51-84 (19 ε4+/16 ε4-).

High CR was associated with better cognition. CR2 was associated with memory and CR3 was predictive of EF. High CR was also associated with greater cortical thickness: CR1 with cingulate; CR2 with inferior and superior parietal; and CR3 with insula, inferior and superior parietal.

Across all CR measures, the interaction of ε4 and CR was associated with insula, inferior and superior parietal thickness. CR2 and CR3 further revealed interactions within frontal regions: CR1 and CR2 were associated with right parahippocampal gyrus (PHG), CR2 with left hippocampus, and CR3 with left PHG. Some regions showed an 'Additive Benefit', where high CR was particularly beneficial to ε4 carriers, while others showed an 'Additive Detriment', where low CR was particularly detrimental to ε4 carriers.

This study also demonstrated that different CR measures yield disparate results. Nevertheless, CR was beneficial to both cognitive functioning and cortical thickness, particularly in ε4 carriers. Results are clinically translatable to identify mechanisms to delay the onset of AD.

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AGING, EXECUTIVE FUNCTION, FRONTO-PARIETAL NETWORK CORTICAL THICKNESS: INSIGHTS FROM COGNITIVE RESERVE

Cognitive reserve (CR) is a theoretical construct designed to explain the nonlinear relationship between brain pathology and clinical symptoms (Stern, 2009), wherein the same neuropathological damage in two individuals can result in differing levels of cognitive disturbance. For example, autopsy research has revealed that up to one third of individuals who meet neuropathological criteria for Alzheimer's disease (AD) do not exhibit cognitive deficits (Esiri et al., 2001). As a result, this subset of individuals engages some form of mechanism(s) to cope with neuronal damage to preclude clinically significant cognitive decline. Individuals with high levels of CR are thought to be more resilient to neurological insults. CR research seeks to understand resilience in both behavioral and neurological manifestations. CR also identifies factors that increase resilience to offset neurological damage and alter the trajectory of cognitive decline. These factors encompass both early developmental characteristics (e.g., socioeconomic status) and modifiable lifestyle characteristics that can occur at later life stages.

CR can be applied to any condition that involves neurological insult, and it is particularly valuable within the context of aging and AD. Through further understanding the resilience in aging, we can identify effective intervention strategies to mitigate cognitive decline and prolong functional independence. Delaying assisted living or nursing home care allows individuals to maintain lifestyle, emotional functioning, social environment, and quality of life. This also has important implications for societal economics, as the cost of care giving for individuals with dementia in 2012 alone was

$216 billion in the U.S. and it is expected to grow each year (Alzheimer's Association, 2013).

CR Theory and Evidence

The theoretical understanding of CR comes from active model theories, which posits that the brain actively works to cope with and compensate for neuropathological damage. These theories focus on neuronal functioning to explain the relationship between known protective factors and clinical symptoms (Stern, 2002). Active model theories use the term 'neural reserve' to refer to the variability in neural networks that reflect performance in healthy individuals. Individual variability may therefore be due to efficiency, capacity, and/or flexibility of brain networks (Stern, 2009). Neural compensation describes 'recruitment' of different brain regions and networks that are activated following brain insult, which are not typically used, or used to the same degree, in healthy individuals (Stern, 2009).

Evidence for active model theories comes from functional MRI (fMRI), which consistently shows that older adults have increased brain activation compared to younger adults (Cabeza et al., 1997a). The Scaffolding Theory of Aging and Cognition (STAC) propose that increased activation in frontal regions is indicative of healthy aging processes. With increased activation, the brain is recruiting other neural networks to achieve a similar cognitive status. Thus, the brain is coping with this damage. However, when scaffolding occurs, neural networks are less efficient and are more susceptible to error (Park & Reuter-Lorenz, 2009). A recent update to STAC, STAC-r, takes a life-span oriented approach to understanding brain functioning in late-life, compared to earlier theories that focused primarily on cross-sectional studies in old age. STAC-r incorporates

several life course variables that can either increase or decrease CR by enhancing or depleting neural resources in both brain structure and brain function. Availability of neural resources thereby influences the ability to engage in compensatory strategies and brain scaffolding, which influences cognitive function and the slope of cognitive changes (Reuter-Lorenz & Park, 2014).

CR Measurement

Multiple factors comprise cognitive reserve. Some factors of CR are influential from early development, while other factors are modifiable lifestyle habits that can be changed throughout mid and late life. The latter factors show promise for efficacious interventions to stave off cognitive decline and maintain functional dependence. Some of the commonly measured CR factors include socioeconomic status (SES), education, occupation, IQ, leisure activities, and nutrition.

There are numerous ways to measure some CR variables. For example, retrospective estimation of SES at childhood and middle adulthood has often been used in addition to current SES as measures of CR (Karlamangla et al., 2009; Karp, 2004; McEwen & Gianaros, 2010). Occupation is frequently coded into a nominal variable based on job complexity and societal rank (Le Carret et al., 2003). IQ is typically measured through a word reading task because verbal intelligence is best preserved with age (McGrew & Flanagan, 1998). Leisure activity is an admittedly broad category that could encompass a wide array of activities. CR researchers typically examine the frequency of engagement in three types of activities because they are thought to help with maintenance of cognitive functioning over time. These include cognitively stimulating activities, physical activity, and social contact (Scarmeas, Levy, Tang, Manly, & Stern,

2001; Sole-Padulles et al., 2009). Finally, nutrition is less-well studied in the context of CR and is typically measured through informal questionnaires assessing the frequency of vitamin supplements or intake of foods rich in particular nutrients, such as vitamins B, C, D, E, and folic acid, which are thought to play a role in late life cognitive function (Bowman et al., 2012; Tucker, Qiao, Scott, Rosenberg, & Spiro, 2005).

To capture the broader influences of CR, several attempts have been made to integrate these variables into a composite factor instead of examining each variable in isolation. This is typically done by including z-scored conversions of the various proxy scores into a Principal Components Analysis (PCA) and using the resulting standardized component score as the metric of CR. For example, Stern's group frequently measures CR using a composite of years of education, word-reading and vocabulary knowledge measures (Stern et al., 2005; Stern et al., 2008). Limitations to this model are that this estimation of CR is primarily based on achievement and intelligence, which are relatively set by early life experience. As such, they do not capture more recent influences of lifestyle factors that are modifiable and as such, have potential for intervention. More sophisticated and broad measures of CR have also begun to appear. One such study incorporated IQ, education/occupation, and leisure activities (Sole-Padulles et al. (2009). IQ was estimated through word reading or vocabulary measures. Education and occupation were operationalized to reflect increasing attainment and complexity (i.e., on an ordinal scale, whether independently or in combination), and leisure activity was assessed using a comprehensive survey of time spent in various activities. While this approach is more comprehensive than earlier achievement-centric approaches, it lacked inclusion of socioeconomic status, nutrition and some possibly relevant leisure activities

and health factors (i.e. time spent sedentary, high blood pressure, etc.). The proposed study seeks to examine different ways to measure CR using both the aforementioned composites and a nuanced composite aimed to account for the noted limitations.

Age-Related Cognitive and Neural Changes

To effectively examine the influence of CR, it is important to distinguish cognitive and neural changes associated with normal aging from those with AD. That is, because cognitive changes occur with both normal aging and AD, it can be difficult to tease apart normal and neurodegenerative processes. For example, memory declines in both normal aging and AD, but they do so differently. In normal aging, memory decline is characterized by reduced free-recall that improves with cueing or under tasks that rely on recognition (Schaie & Willis, 2010). In contrast, AD is associated with more dramatically impaired recall that does not improve with cueing or recognition testing (Tierney et al., 2001).

Memory changes are associated with age-related volume loss in the hippocampus and medial temporal lobes, regions critical for transfer of information from short-term memory to long-term storage (Bergfield et al., 2010; Schaie & Willis, 2010). The degree of volume loss in these regions is significantly less in normal aging than in mild cognitive impairment (MCI), a prodromal categorization of AD, and in AD (Du et al., 2001; Frisoni et al., 2002). Memory declines are the hallmark symptom of AD (American Psychiatric Association, 2013). However, intervention efficacy is less likely if started after significant memory decline is apparent because extensive structural and functional impairments precede objective memory impairment (Tomadesso et al., 2015). Thus, earlier and subtler markers of cognitive decline than memory performance must be

targeted in order to have the potential for effective intervention, making it more difficult to effectively intervene. That memory changes are associated with large brain changes, it is likely that there are more subtle markers of cognitive decline than memory.

Functional MRI (fMRI) has informed our understanding of age-related neural changes. fMRI works by examining the blood oxygenation level-dependent (BOLD) signal, which is a measure of change in deoxygenated blood to oxygenated blood and thus, a proxy for neuronal activity (Arthurs & Boniface, 2002). fMRI studies consistently find that older adults exhibit increased brain activation compared to younger adults (Cabeza et al., 1997a), which is thought to be due to compensation for neural degradation or, as STAC theory would describe it, scaffolding (Park & Reuter-Lorenz, 2009). A review of the AD literature (Sperling et al., 2010) specifically showed that increased frontal activation is typically associated with decreased activation in the hippocampus during an episodic memory task. Thus, as the AD neuropathology progresses in the hippocampus, frontal region activation increases in an apparent attempt to reorganize or compensate (Sperling et al., 2010).

Emerging Role of EF in Prodromal AD

There is increasing evidence that age-related memory declines may be partially explained by declines in EF. This is the basis of the executive decline theory of cognitive aging (Crawford, Bryan, Luszcz, Obonsawin, & Stewart, 2000; Dempster, 1992; Parkin, 1997). This theory draws on neurobiological research that shows the first neural changes associated with aging are evident in frontal regions, which would therefore be expected to relate to EF changes, rather than memory decline (Crawford et al., 2000). It is thought that these early EF changes are associated with recruitment of cognitive processes to

organize memory function (Ferrer-Caja, Crawford, & Bryan, 2002). Initial tests of this theory using fMRI in healthy older adults with intact general cognitive and memory performance demonstrated early functional compensatory activation that was based specifically on both age and executive functioning ability (Nielson, Langenecker, & Garavan, 2002). Indeed, after controlling for general cognitive abilities, EF has been shown to uniquely account for the age-related variance in recall and recognition (Crawford et al., 2000; Ferrer-Caja et al., 2002). Furthermore, white matter hyperintensities have been associated with episodic memory performance with the relationship mediated by EF performance (Parks et al., 2011). Hippocampal volume has further been associated with EF performance (Parks et al., 2011). Therefore, memory abilities appear to rely on EF functions.

Recent longitudinal research shows that EF changes precede memory changes. . Specifically, a longitudinal study showed that participants who had lower scores on tests of color-word interference and verbal fluency showed global decline one year later (Clark et al., 2012). Furthermore, EF measures are more predictive of later global cognitive decline (Clark et al., 2012) and conversion from MCI to dementia (Aretouli, Tsilidis, & Brandt, 2013) than baseline memory scores. A longitudinal study of elderly women suggested that executive dysfunction may precede memory changes by approximately 3 years (Carlson, Xue, Zhou, & Fried, 2009).

EF is a broad construct that encompasses several abilities, including planning, initiation, inhibitory control, flexibility, attention, working memory and vigilance (Niendam et al., 2012). Research on different facets of EF has shown that performance on the color-word interference test, a measure of inhibitory control, predicted future

cognitive decline in healthy older adults (Clark et al., 2012). Inhibitory control reflects the ability to suppress information that is not pertinent to the current task (Cabeza, Nyberg, & Park, 2005) and may prove to be a more sensitive measure to changes in EF and later cognitive decline (Hasher & Zacks, 1988).

Furthermore, decline in executive functions is related to impairment in instrumental ADLs (IADLs), such as driving, financial management, medication management, food preparation, housekeeping, and other abilities that allow older adults to live independently (Jefferson, Paul, Ozonoff, & Cohen, 2006). Furthermore, this study showed that inhibitory control is equally related to all IADLs, not simply one or two tasks. This indicates that inhibitory control is key to maintaining functional independence (Jefferson et al., 2006). The relationship of general EF with IADLs is long established (Cahn-Weiner, Boyle, & Malloy, 2002; Marshall et al., 2011), but the idea that inhibitory control in particular explains this relationship provides us with a more specific understanding of this relationship with specific intervention targets to help maintain inhibitory control with the goal of prolonging functional independence.

The frontoparietal neural network (FPN) is hypothesized to underlie executive functions, and consists of the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), inferior and superior parietal cortices, and insular cortex (Grandjean et al., 2012). Connectivity analyses show that during EF tasks, the lateral frontal region communicates with regions in the dorsal attention network and default mode network (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). This degree of communication with the FPN and other networks is interpreted as evidence that the FPN orchestrates neural activity to subserve general EF performance. Indeed, the

FPN has also been shown to be active during an array of other executive functioning tasks including those requiring attentional control (Li, Gratton, Fabiani, & Knight, 2013; Shomstein, Kravitz, & Behrmann, 2012), planning (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010), and response inhibition (Steele et al., 2013).

Structural changes, evidenced by anatomical MRI, in the FPN are also associated with performance on measures of EF. For example, greater cortical thickness in the DLPFC, IFG, and superior parietal gyrus has been associated with better performance on the Wisconsin Card Sorting Test (Burzynska et al., 2012) in healthy older adults. Furthermore, cortical thickness in the DLPFC has differentiated high and low performers in both healthy young adult and older age groups, indicating that the structure of this region may be a more sensitive measure than EF performance to age-related change (Burzynska et al., 2012). In addition, insula volume is related to EF performance on measures of the Stroop test, digit span, and the Trail-making Tests (Ruscheweyh et al., 2013).

The Role of Apolipoprotein-E in Risk for AD

There are known risk factors for AD that are important to include to aid a comprehensive understanding of predicting and intervening in this neurodegenerative process. Age is the largest risk factor to developing AD. Indeed, AD symptoms most typically onset around age 65 with incidence incrementally increasing thereafter (Association, 2013). The ε4 allele of the Apolipoprotein-E gene (ApoE) is a well-recognized risk factor for developing AD. ApoE is a lipid transport protein that metabolizes triglycerides and cholesterol and is involved in axon regeneration and remyelination. Presence of the ε4 allele increases the risk for AD through inhibiting

clearance of toxic substances from the brain (Huang & Mucke, 2012). Compared to non-carriers, healthy older adults who carry the ε4 allele exhibit greater declines in memory (Caselli et al., 2004), disrupted resting state neural connectivity (Machulda et al., 2011) and reduced cortical thickness in the hippocampus and medial temporal regions (Burggren et al., 2008), all of which are considered to be risk factors for developing AD.

Although ApoE-ε4 confers a greater risk of AD, some samples show only 40% of those with AD carry the ApoE-ε4 allele, compared to 15% of controls (Sando et al., 2008). Hence, 60% of those diagnosed with AD may not carry a genetic predisposition, while 15% of cognitively intact adults have a genetic vulnerability, but do not show cognitive impairment. Therefore, while it is important to understand the influence of the ε4 allele on cognitive and neural changes associated with aging and AD, it does not fully explain the incidence of AD. Moreover, it appears that other factors likely modify the relationship of ε4 inheritance and cognitive decline. For example, education offsets the risk of future cognitive decline by ε4 over 6 years in adults who were healthy at baseline (Shadlen et al., 2005). Therefore, other factors, such as CR, likely explain this disparity.

Cortical Thickness as an AD Biomarker

Cortical thickness is a minimally invasive and less expensive tool that is sensitive to cognitive and neuropathological symptoms of dementia (Apostolova et al., 2012; Devanand et al., 2007; Dickerson & Wolk, 2012; Jack et al., 2011; Whitwell et al., 2007), including tau and amyloid beta protein deposition (Desikan et al., 2009) and conversion to AD (Gomar et al., 2011). While cortical thickness is also indicative of underlying pathology in elders, it also increases with intervention (Lampit, Hallock, Suo, Naismith, & Valenzuela, 2015; Reiter et al., 2015) even in brief 8-week interventions (Engvig et al.,

2010). The reviewed studies indicate that cortical thickness is a useful measure to detect subtle changes in relatively short periods of time.

The Present Study

The proposed study seeks to examine the influence of CR on measures of EF and neural integrity, with an emphasis on subtle indicators that might index future decline in healthy older adults. Through examining subtle biomarkers, it is possible to identify an optimal time to implement interventions before irreversible and macro neuronal damage has occurred. We would also like to understand the relationship of CR with the ε4 allele and if high CR mitigates the negative influence of carrying the ε4 allele. CR measurement is heterogeneous and often bound to achievement-based variables to measure CR, including education, occupation, and IQ (Barulli, Rakitin, Lemaire, & Stern, 2013; Bastin et al., 2012; Liu, Cai, Xue, Zhou, & Wu, 2013; Stern et al., 2008), although CR theory purports this construct encompasses a wide array of other lifestyle factors including SES, diet, and leisure activities (Stern, 2009; Tucker & Stern, 2011). Thus, achievement-based CR measurements represent a disparity in the theoretical construct of CR and its application in the literature. Therefore, the current study examined 3 CR proxies:

1. CR1 was achievement focused and comprised of education and verbal IQ (Stern et al., 2005)
2. CR2 included leisure activities and achievement measures and was comprised of education, verbal IQ, occupation, and leisure activities (Sole-Padulles et al., 2009)

3. CR3 was created in our laboratory and added health functioning (hip-waist ratio, blood pressure, and nutrition) to achievement and leisure activities.

The current study focused on EF and the hypothesized brain regions that subserve these functions. There is evidence that CR is related to verbal and category fluency, and inhibitory control (Roldan-Tapia, Garcia, Canovas, & Leon, 2012). Furthermore, early evidence shows that EF might mediate the relationship between CR and better functional ability in late life (Puente, Lindbergh, & Miller, 2015). To accompany an in-depth understanding of CR, the current research investigated the role of CR and the ε4 allele on structural integrity of the FPN due to its known relationship to a variety of executive functions (Grandjean et al., 2012; D. Li et al., 2013; Shomstein et al., 2012; Spreng et al., 2010). Regions associated with the FPN include the DLPFC, ACC, IFG, insula, and superior and inferior parietal cortices (Grandjean et al., 2012).

Specific Aims and Hypotheses

This study sought to examine the relationship of ε4 and CR on executive functions and FPN cortical thickness

1. Neuropsychological performance:
    A. It was expected that there interaction effects between CR and ε4 inheritance would be observed, such that presence of at least one ε4 allele (ε4+) would negatively influence cognitive functioning, unless participants are in the high CR group. It was expected that high CR would attenuate the negative influences of ε4 inheritance. Furthermore, it was expected that this effect would be specific to EF and not influence memory domains.

B. Results were expected to vary based on CR proxy. It was expected that more inclusive CR proxies would show more relationships to executive functions, such that CR1 and CR2 would show relationships to EF in some measures while CR3 would be related to more EF measures

2. Cortical thickness:

A. CR and ε4 inheritance were expected to interact in FPN regions, including ACC, DLPFC, inferior frontal gyrus, inferior and superior parietal cortex and insula (Grandjean et al., 2012). ε4 was expected to be associated with reduced FPN thickness in the low CR group. It was expected that there would be no difference between the ε4 groups in the high CR group, thereby indicating intact structural FPN. CR and ε4 inheritance were not expected to have a statistically significant effect on medial temporal cortical thickness and hippocampal volume in this healthy elder sample.

B. Similar to neuropsychological performance, it was expected that the interaction effects of CR and ε4 inheritance would be more apparent in CR3 and the least apparent in CR1.

METHOD

Participants

The proposed research is part of a larger study that is funded by grants from Drs. Kristy Nielson and Anthony Porcelli. Approval from the Marquette University and Medical College of Wisconsin Institutional Review Boards were obtained. Inclusion criteria for this study were right-handedness and minimum age of 45 years. Exclusionary criteria were MRI safety hazards, cardiac disease (untreated hypertension, arrhythmia, carotid artery disease), neurological disease (cerebrovascular disease, dementia or

cognitive impairment, head trauma with loss of consciousness >30 mins, chronic meningitis, multiple sclerosis, pernicious anemia, normal-pressure hydrocephalus, HIV infection, Parkinson's disease, and Huntington's disease), endocrine disorders (renal disease, insulin-dependent diabetes), major psychiatric disturbance that meets criteria for DSM-IV axis I disorders, Mini-Mental State Exam (MMSE) score < 26, Geriatric Depression Scale score <12, substance abuse history, use of beta-blockers, and use of nicotine products.

Participants were recruited from the local community via newspaper and email advertisements. Thirty-seven adults between ages 51-84 participated in neuropsychological testing, MRI scanning, and genotyping. Eighteen participants were carriers of at least 1 ε4 allele (ε4+), while nineteen participants were non-carriers (ε4-).

Materials

Demographic and Medical History. Demographic and medical history information was assessed using a survey from our laboratory that includes items regarding age, education, occupation, race, ethnicity, socioeconomic status, medical diagnoses, medications, and physical functioning.

The Trail-Making Tests (Reitan & Wolfson, 1986), part A (TMT-A) and part B (TMT-B). TMT-A required participants to sequence numbers from 1-25 on a piece of paper by drawing a line from one to the other as quickly as possible. TMT-B required participants to sequence numbers and letters, in alternating order. This test assesses visual search, scanning, processing speed, and mental flexibility.

Rey Auditory Verbal Learning Test (Rey, 1958). The AVLT is a test of verbal learning and memory. A list of 15 words was read to the participant over five consecutive

encoding-retrieval trials. A second list of 15 words was read as a distraction afterward. Directly following the distracter trail list, participants were asked to recall the first list of words. Recall was tested again after a 20-minute delay. A yes/no recognition paradigm was also presented after recall at the 20-minute delay.

North American Adult Reading Test (Blair & Spreen, 1989)). The NAART is a test of word reading that serves as a proxy for premorbid IQ. Participants were instructed to read a list of 61 words of increasing difficulty.

Wisconsin Card Sort Test (Grant & Berg, 1948). The WCST is a measure of task switching, perseveration, and mental flexibility. Participants were presented with 4 key cards of different color, shape, and number of items. Participants were asked to sort a deck of cards that vary based on color, shape, and number of items but no instructions are given for how to sort the cards. Verbal feedback was given after each card. The unannounced rule changes occur after 10 correct sorts, requiring participants to adapt to the new rule. The task ended when 128 cards were sorted or if the participant achieved 6 correct categories (2 of each color, shape, and number).

Controlled Oral Word Association Test (COWA) (Benton, 1967). The COWA task measures verbal fluency by instructing participants to name as many words as possible that begin with a certain letter within 60 seconds. Participants were instructed to avoid proper names and obvious close approximations of prior answers (e.g., fish, fishing, fisherman). Three trials were completed with the letters F, A, and S.

Category Fluency (Goodglass & Kaplan, 1983). Category fluency measures verbal fluency for semantic categories. Participants were instructed to generate as many different animals as possible in 60 seconds.

Leisure Activities Questionnaire (LAQ). The LAQ was developed in our laboratory and includes an inventory of a variety of leisure activities including social activities, mentally demanding activities, physical activities, cultural activities, and leadership/work activities. Both hours per week and mental demand from 1 (not at all demanding) to 10 (extremely demanding) were recorded for each participant.

Nutrition Survey. The Nutrition Survey was developed in our laboratory to measure the frequency of food consumption in multiple categories of items that are rich in vitamins B, C, D, E, and folates. The survey is measured on a scale of 0-3 for consumption of each food item (0=never, 1=once per month, 2=once per week, 3=several times per week). Items rich in common nutrients are summed together to create scales of vitamins B6, B12, D, E, and folates.

CR measurement. The current study examined CR in 3 ways. The first two metrics are composite scores frequently used in the literature. CR Composite 1 (CR1) included years of education and NAART score as the proxies for CR (Stern et al., 2005; Stern et al., 2008). All variables were standardized and submitted to a Principal Components Analysis (PCA), with the resulting standardized factor score used in further analysis as the component score.

CR Composite 2 (CR2) includes three proxies of CR: IQ, an education/occupation measure, and a leisure activities variable (Sole-Padulles et al. (2009). IQ was measured with the NAART. We used the same coding scheme used in the literature to create the 7-point education/occupation scale (education: 0 = no formal education, 1 = primary school, 2 = secondary education and 3 = superior or university education and as regards occupation; occupation: 0 = non-qualified manual, 1 = qualified manual, 2 = qualified

non-manual or technician, 3 = professional (university degree required), 4 = manager or director (university degree required). The specific measure of leisure activities used by Sole-Padulles and colleagues was unpublished. Therefore, we composed a similar scale using the LAQ, including sums of cognitively stimulating activities (i.e., reading, writing, playing music, and painting), physical activities (i.e., sports, walking), and social engagement activities (participating in social activities, groups, associations, and volunteer work). One point was given for each activity that is completed on a weekly basis, to create a 9-point scale. The scores from each of the three proxy variables was standardized and submitted to a PCA, with the resulting standardized factor score used in further analysis as the composite score.

CR Composite (CR3) was similar to the CR2 composite but designed to better match the theoretical understanding of CR by broadening the existing composite scores and including a health proxy. As the existing CR variables, the first proxy was a verbal IQ estimate with the NAART. A 9-point education/occupation scale was created to better fit our sample (education: 1=0-8 years, 2=9-12 years, 3=13-15 years, 4=16 years, 5=>16 years; occupation: 1=manual, 2=qualified non-manual/technician/retail, 3=professional positions, 4=manager/director/intellectual). Similar to CR2, leisure activities were assessed with LAQ but CR3 included additional types of activities in each composite and 2 additional leisure activity domains. As before, 1 point was assigned to each activity completed regularly. Specific leisure activities included sums of cognitively stimulating activities (i.e., reading, writing, painting, playing music, listening to music, handicraft, bingo, playing solitaire, crossword puzzles, maintaining a collection, managing finances, following the stock market, driving, using a computer, and attending courses), physical

activities (i.e., sports, walking, outdoor activities, gardening, cooking, and shopping), social engagement activities (i.e. participating in social/family activities, participating in a club, eating out, playing games with others, and telephone conversations), cultural activities (i.e. attending theatres/concerts, religious groups, political or cultural interests, going to museums or exhibitions, painting, drawing, photography), and work/leadership activities (i.e. childcare, supervising others, government, trade, or political work, teaching classes). Finally, the health proxy included several factors related to vascular functioning. Of note, the coding for the following variables was designed to be consistent with the previous CR proxies, such that higher numbers indicate better health and thus greater CR. The health proxy included hip-waist ratio that was dichotomized into risk for metabolic complications according to the World Health Organization (Organization, 2011) (males: 1 = < .90, 2 = >. 89; females: 1 = <.85, 2 = > .84), resting blood pressure split into 3 categories according to standards from the American Heart Association (Association, 2017): Systolic blood pressure: 0 (hypertensive) = >140, 1 (pre-hypertensive) = 120-139, 2 (normal) = <79; Diastolic blood pressure: 0 (hypertensive) = >90, 1 (pre-hypertensive) = 80-89, 2 (normal) = <79. Finally, the health proxy included nutrition measured by the Nutrition Scale to assess frequency of foods rick in vitamins B6, B12, B, C, D, and Folates. Surveyed foods that were consumed at least weekly were assigned 1 point and the sum of all foods was totaled into a nutrition scale. If participants were taking a supplement, 2 points were assigned to the total score based on the increased amount of intake compared to a typical serving of the given food.

Physiological Measures. Several measures of physiological functioning were taken, including measurement of hip and waist circumference and resting systolic and diastolic blood pressure.

MRI Scanning. MRI scanning was performed on the GE 3.0 Tesla 750 short-bore MRI scanner. All images were obtained using a standard head coil. High-resolution, three-dimensional spoiled gradient-recalled at steady-state (SPGR) anatomic images were acquired (TE = 3.2 ms; TR = 8.3 ms; flip angle = 12°; number of excitations (NEX) = 1; slice thickness = 1.0 mm; FOV = 192 cm; resolution = 256 × 256 matrix).

Procedure

Data collection relevant for the proposed research occurred in two sessions. The first session took place at Marquette University. Informed consent and MRI safety screening were obtained at the beginning of the first session followed by neuropsychological testing and physiological measures, such as hip-waist ratio and resting blood pressure. Demographics surveys were also completed in session. Additional self-report measures were completed at home and returned to the next session.

The second session took place at the Pavilion in the Medical College of Wisconsin and consisted of a 75-minute MRI session. Prior to the MRI scanning sessions, MRI safety screening information was reviewed again. Additionally, participants were oriented to the scanning environment with the option to use the MRI simulator. Prior to the scan, all participants underwent practice versions of each task that was presented in the MRI. Participants were compensated $15 per hour.

Analyses

Aim 1: Neuropsychological Data. ANCOVA analyses were conducted to understand the influence of CR and ε4 inheritance on the neuropsychological data. Median splits of CR1, CR2, and CR3 factor scores were conducted to split groups into high and low CR. For each CR factor, seven sets of 2x2 ANCOVAS included the factors CR group (High CR, Low CR) and genetic risk group (ε4+, ε4-), covarying for age and the neuropsychological factor scores as the dependent variable. For each model that showed a statistically significant main or interaction effect, a post hoc hierarchical regression was conducted to further explore this relationship. Specifically, to predict the factor score, 4 steps were included in the model where Step 1 was age, Step 2 was ε4 inheritance, Step 3 was CR, and Step 4 was the interaction term of CR and ε4. To compute the interaction term, CR was centered and multiplied with ε4 in heritance (0=ε4-, 1=ε4+).

Aim 2 FPN and MTL/Hippocampal Cortical Thickness Per Label. To compare FPN and MTL/hippocampus integrity, these regions were extracted for each subject. FPN regions outlined by Grandjean et al. (2012) associated with the Desikan-Killiany atlas provided in FreeSurfer include rostral middle frontal gyrus (MFG), caudal anterior cingulate cortex (ACC), rostral ACC, pars opercularis, pars triangularis, pars orbitalis, superior parietal, and insula. Desikan-Killiany atlas regions associated with the MTL include the entorhinal cortex and parahippocampal gyrus (PHG) in addition to bilateral hippocampal (HC) volume. Median splits of CR1, CR2, and CR3 factor scores were conducted to split groups into high and low CR. For each CR factor, twelve sets of 2x2 ANCOVAS for each hemisphere included the median split of CR factor scores (High

CR, Low CR) and genetic risk group (ε4+, ε4-). Cortical thickness for each FPN and MTL/HC was the dependent variable and each model covaried for age. For each model that showed a statistically significant main or interaction effect, a post hoc hierarchical regression was conducted to further explore this relationship. Specifically, to predict the cortical thickness in each label, 4 steps were included in the model where Step 1 was age, Step 2 was ε4 inheritance, Step 3 was CR, and Step 4 was the interaction term of CR and ε4. To compute the interaction term, CR was centered and multiplied with ε4 in heritance (0=ε4-, 1=ε4+)

Aim 2 FPN and MTL Cortical Thickness Per Vertex. To better localize the relationship of ε4 and CR, a mask of the FPN and MTL regions was created and a general linear model (GLM) was conducted at each vertex. Unfortunately, only cortical regions could be included in the mask and thus the hippocampus was not included in the vertex analysis. Given the small sample size, the analyses included CR1, CR2, and CR3 as a continuous variable to maximize statistical power. For each CR variable, The GLM examined the correlation difference of cortical thickness and CR between ε4- and ε4+ covarying for age. False Discovery Rate (FDR) was applied to correct for multiple comparisons. Red regions indicate a greater correlation of CR and cortical thickness within ε4-; Blue regions indicate a greater correlation of CR and cortical thickness within ε4+. For regions of significance, a label was created on an averaged surface and converted to each subject's surface. Cortical thickness for each region of significance was extracted. A post hoc hierarchical regression was conducted to predict cortical thickness in each region of significance where Step 1 was age, Step 2 was ε4 inheritance, Step 3

was CR, and Step 4 was the interaction term of CR and ε4. To compute the interaction term, CR was centered and multiplied with ε4 in heritance (0=ε4-, 1=ε4+)

RESULTS

Participants

Of the original sample of 37 adults between the ages of 51-84, 2 participants were excluded from the final analyses (1 due to claustrophobia during the MRI session; 1 due to unusable MRI data. The final sample consists of 35 adults between the ages of 51-84. Nineteen participants are ε4+ and sixteen participants are ε4-. See Table1 for demographic characteristics of the final sample.

Cognitive Reserve Factors

CR1. Years of education and NAART scores were standardized and submitted to a factor analysis using PCA with Equamax rotation and inputted into 1 fixed factor. Factor scores were extracted using the Anderson-Rubin method. The analysis revealed that the factor explained 66.98% of the variance for the set of variables. See Table 2 for details.

CR2. NAART scores, the 7-point education/occupation scale, and the 3-domain leisure activities sum (cognitively stimulating, social, and physical) were standardized and submitted to a factor analysis using PCA with Equamax rotation and inputted into 1 fixed factor. Factor scores were extracted using the Anderson-Rubin method. The analysis revealed that the factor explained 57.47% of the variance for the set of variables. See Table 2 for details.

CR3. NAART scores, the 9-point education/occupation scale, and the 5-domain Leisure Activities sum (cognitively stimulating, social, and physical, cultural, and

work/leadership), hip-waist ratio, systolic blood pressure, diastolic blood pressure, and nutrition totals were standardized and submitted to a factor analysis using PCA with Equamax rotation and inputted into 1 fixed factor. Factor scores were extracted using the Anderson-Rubin method. The analysis revealed that the factor explained 32.25% of the variance for the set of variables. See Table 2 for details.

Neuropsychological Assessment Factors

Scores from the neuropsychological assessments, including tests of memory (AVLT, Logical Memory), attention, processing speed, working memory (digit span, Trails A, COWA, Digit Copy, SDMT), and executive functions (Trails B, WCST) were standardized. All variables were examined for skewness and kurtosis. Variables that were not normally distributed (i.e. skew < 2.0 and kurtosis < 7.0 (Hoelzle, Meyer, Weiner, Schinka, & Velicer, 2013), including Trails B, WCST conceptual responses, Digit Copy, and SDMT underwent square root transformations. Standardized and transformed variables were submitted to a factor analysis using PCA with Equamax rotation. Individual factors were extracted factors based on eigenvalues greater than 1. Scores were extracted using the Anderson-Rubin method. The analysis revealed 7 components that cumulatively explained 83.98% of the population. Based on variable loadings greater than 0.5, Factor 1 was labeled AVLT with high loadings on AVLT Learning, AVLT Immediate Recall, and AVLT Delayed Recall. Factor 2 was labeled COWA and number of responses to the letter cues of F, A, and S, loaded highest on this factor. Factor 3 was labeled TMT-SDMT as the variables that loaded the highest were Trails A and B, and SDMT. Factor 4 was labeled WCST due to the high loadings of the WCST variables, including Total Errors, Perseverative Responses, and Conceptual Responses. Factor 5

was labeled Logical Memory as Logical Memory Immediate and Delayed recall loaded highest. Digit Span Forward and Backward loaded highest on Factor 6 and therefore this factor was labeled Digit Span. Finally, Digit Span Sequencing and Digit Copy loaded highest on Factor 7. See Table 3 for details.

Aim 1: Neuropsychological Performance

CR1 and Neuropsychological factor scores. Seven 2(CR1) x 2(ε4) ANCOVAs were conducted, covarying for age, were performed to assess the relationship of ε4 inheritance and CR1 with each of the seven factors from the neuropsychological PCA. Where the TMT-SDMT factor was the dependent variable in the 2(CR1) x 2(ε4) ANCOVA, the CR1 main effect showed a statistical trend toward significance ($F(1, 33)= 4.0$, $p=0.06$). Age had a statistically significant effect ($F(1, 33)= 8.6$, $p<0.05$), where greater age was associated with reduced performance on the TMT/SDMT factor. The main effect of ε4 inheritance ($F(1, 33)= 0.30$, $p=0.59$) and ε4 x CR interaction effect ($F(1, 33)= 0.18$, $p=0.68$) was non-significant. See Table 4, section 3, for details. A post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR1, Step 4=CR1xε4 inheritance interaction term) was conducted to better understand the results. Results of the regression revealed statistically significant contributions to the overall model at Step 1 ($F(1, 33)= 8.47$, $p<0.05$) and Step 3 ($R^2\Delta=0.10$, $\beta=0.31$; $p=0.05$). Age explained 20.4% of the variance in TMT/SDMT factor scores and results indicated that high scores (i.e., faster response times) on the TMT/SDMT factor were associated with younger ages ($\beta= -0.45$, $p= 0.01$). CR1 explained an additional 9.6% of the variance in the dependent variable; high CR1 was associated with high scores on the TMT/SDMT factor ($\beta= 0.31$, $p= 0.05$). See Table 5 for details. Overall, both age and CR1 were

predictive of TMT/SDMT factor scores where age played a negative effect and high CR was associated with better performances than low CR.

No other statistically significant main or interaction effects were observed in the remainder of the CR1 ANCOVAs with neuropsychological PCA factors as the dependent variables. See Table 4, sections 1, 2, 4, 5, 6, and 7 for details.

CR2 and Neuropsychological factor scores. Seven 2(CR2) x 2(ε4) ANCOVAs were conducted, covarying for age, were performed to assess the relationship of ε4 inheritance and CR2 with each of the seven factors from the neuropsychological PCA. CR2 showed a statistically significant main effect in the AVLT ANCOVA, ($F(1, 33)= 4.212$, $p=0.05$). See Table 6 section 1 for details. A post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR2, Step 4=CR2xε4 inheritance interaction term) was conducted to better understand the results. Results of the regression revealed a statistically significant contribution to the model at Step 3 $R^2\Delta=0.12$, $p<0.05$). CR2 explained 19.5% of the dependent variable ($\beta=0.35$, $p=0.04$) and indicated that those with high CR had high factor scores (i.e., better performance) on the AVLT component. See Table 7 row A, for details.

The FAS ANCOVA results revealed a statistically significant interaction effect of CR2 and ε4 inheritance ($F(1, 33)= 7.22$, $p<0.05$). Within the high CR2 group, ε4+ had higher FAS factor scores and better performance than ε4- ($t(15)= -3.41$, $p<0.01$). There was no difference between ε4 inheritance groups within the low CR2 group ($t(16)= 1.15$, $p=0.27$). See Figure 1 and Table 6 row 2, for details. A post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR2, Step 4=CR2xε4 inheritance

interaction term) revealed that a statistical trend toward significance at Step 4 with the ε4xCR interaction term ($R^2\Delta$=0,11, β=0.38, p=0.06). CR alone (β=0.08; p=0.44) and ε4 (β=0.15, p=0.41) did not significantly contribute to the model. See Table 7 row B, for details. Results showed that the interaction of ε4 and CR2 was most predictive of the FAS Factor Score; within participants with high CR, ε4 carriers had higher factor scores and faster completion times on TMT/SDMT than non-ε4 carriers with high CR.

Results of the TMT/SDMT ANCOVA showed that age had a statistically significant effect (F(1, 33)= 7.89, p<0.05). See Table 6 row 3, for details. Post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR2, Step 4=CR2xε4 inheritance interaction term) revealed that age significantly contributed to the model at Step 1 (F(1, 33)=8.47, β=-0.45, p<0.05), indicating that those with high factor scores were younger. See Table 7 row C, for details.

Results of the Logical Memory ANCOVA revealed a statistically significant main effect of CR2 (F(1, 33)=6.41, p<0.05). See Table 6 row 5, for details. The post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR2, Step 4=CR2xε4 interaction term) revealed a statistically significant contribution to the model at Step 3 ($R^2\Delta$=0.16, p<0.05), and indicated that those with high CR2 (β=0.41, p<0.05) had high factor scores and better performance. See Table 7 row D, for details.

No statistically significant results were observed for the WCST, DSF/DSB, and DSS/DigCopy neuropsychological factors. See Table 6 sections 4, 6, and 7 for details.

CR3 and Neuropsychological factor scores. Seven 2(CR3) x 2(ε4) ANCOVAs were conducted, covarying for age, were performed to assess the relationship of ε4

inheritance and CR3 with each of the seven factors from the neuropsychological PCA. Results from the TMT/SDMT ANCOVA revealed a significant main effect of CR3 (F(1, 33)= 4.68, p<0.05) and age (F(1, 33)=3.86, p=0.06). See Table 8 section 3, for details. The post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR3, Step 4=CR3xε4 interaction term) revealed statistically significant contributions at Step1 (F(1, 33)=8.47, p<0.05) and Step 3 ($R^2\Delta$=0.10, p<0.05). Age explained 20.4% of the variance in the TMT/SDMT factor (β= -0.45, p=0.06); high scores on this factor were associated with younger ages. CR3 explained 10.0% of the variance in TMT/SDMT (β= 0.37, p<0.05); High CR was associated with higher factor scores (See Table 9 row A). Overall, analyses showed that CR3 and age contribute most to the TMT/SDMT factor score; younger ages and high CR3 were associated with better performances.

Results from the WCST factor revealed a statistically significant main effect of CR3 (F(1, 33)= 8.77, p<0.05 (Table 8 section 4). The post hoc hierarchical regression analysis (Step 1=age, Step 2=ε4 inheritance, Step 3=CR3, Step 4=CR3xε4 interaction term) revealed statistically significant contributions to the model at Steps 3 ($R^2\Delta$=0.23, p<0.01) and Step 4 ($R^2\Delta$=0.11, p<0.05). CR3 explained 22.8% of the variance in the dependent variable (β=0.51, p=0.04); those with high CR had high factor scores. Inclusion of the CR3xε4 interaction term explained 10.5% of the variance in the dependent variable (β=-0.39, p<0.05). See Table 9 row B. Post hoc t-tests indicated that those with high CR3 had higher scores on the WCST factor (mean difference= -0.81, t(33)= -2.53, p<0.05), though factor scores were not significantly different within the low CR3 group (t(15)= -0.20, p=0.85) or the high CR3 group (t(16)= 0.78, p=0.45). Analyses indicated that CR3 alone and the interaction of CR3 and ε4 inheritance were predictive of

WCST factor scores; those with high CR3 had better performances than those with low CR3, however, post hoc analyses did not show a meaningful difference between ε4 inheritance groups within CR groups.

No statistically significant results were observed for the AVLT, FAS, LogMem, DSF/DSB, and DSS/DigCopy factors. See Table 8 sections 1, 2, 5, 6, and 7 for details.

Aim 2: FPN and MTL/Hippocampal Cortical Thickness

Label Analyses

Twelve 2(CR1) x 2(ε4) ANCOVAs, covarying for age, were conducted per hemisphere to assess the relationship of ε4 inheritance and CR1 on cortical thickness in the FPN, MTL, and hippocampus. Post-hoc analyses were conducted for regions that showed statistically significant main or interaction effects, including t-tests and hierarchical regression analysis predicting cortical thickness (Step 1=age, Step 2=ε4 inheritance, Step 3=CR, Step 4=CR x ε4 interaction term).

CR1 and cortical thickness per label. A main effect of CR1 was observed in the right caudal ACC ($F(1, 33)=4.45$, $p<0.05$) (See Table 10, panel 2, row B). The post hoc hierarchical regression analysis predicting right caudal ACC cortical thickness (Step 1=age, Step 2=ε4 inheritance, Step 3=CR1, Step 4=CR1xε4 interaction term) revealed a statistically significant contribution to the model at Step 3 ($R^2\Delta=0.13$, $p<0.05$). CR1 ($\beta=0.36$, $p<0.05$) explained 12.8% of the variance in caudal ACC cortical thickness and indicated that those with high CR1 had greater cortical thickness than those with low CR1 (See Table 11).

CR1, ε4, or CR x ε4 did not show statistically significant main or interaction effects in the remainder of the FPN, MTL, or hippocampus. See Table 10 (row A, row B panel 1, rows C-I) and Table 12 for details.

CR2 and Cortical Thickness Per Label. Interaction effects of CR2 and ε4 were observed in 8 of the 12 regions, including the left rostral MFG ($F(1, 33)= 8.70$, $p<0.01$) (Table 13, panel 1, row A), left pars opercularis thickness ($F(1, 33)=6 .61$, $p<0.05$) (Table 13, panel 1, row D), left pars triangularis ($F(1, 33)= 5.51$, $p<0.05$) (Table 13, panel 1, row F); left inferior parietal ($F(1, 33)= 4.89$, $p<0.05$) (Table 13, panel 1, row G), left insula ($F(1, 33)= 5.02$, $p<0.05$) (Table 13, panel 1, row I), right inferior parietal ($F(1, 33)= 4.38$, $p<0.05$) (Table 13, panel 2, row G), right insula ($F(1, 33)= 5.31$, $p<0.05$) (Table 13, panel 3, row I), and left hippocampus ($F(1, 33)= 5.77$, $p<0.05$) (Table 14, panel 1, row A).

Post hoc hierarchical regression analyses revealed that neither CR2 nor ε4 alone significantly predicted cortical thickness in FPN regions. However, the interaction term of CR2 and ε4 significantly contributed to the model at Step 3 in the left rostral MFG ($R^2\Delta=0.17$, $p<0.05$) (Table 15, row A), left pars opercularis ($R^2\Delta=0.16$, $p<0.05$) (Table 15, row B), left pars triangularis ($R^2\Delta=0.17$, $p<0.05$) (Table 15, row C), and left inferior parietal ($R^2\Delta=0.15$, $p<0.05$) (Table 16, row A). The interaction term did not predict cortical thickness in the left insula (Table 16, row B), right insula (Table 16, row C) or volume in the left hippocampus (Table 17).

Post hoc t-tests revealed that within the high CR group, ε4+ had greater cortical thickness than ε4- in the left rostral MFG ($t(15)= -2.58$, $p<0.05$) (Figure 2, panel A, row 1), left insula ($t(15)= -2.17$, $p<0.05$) (Figure 2, panel A, row 2), and a trend in this

direction for the left pars triangularis ($t(15)= -1.98$, $p=0.07$) (Figure 2, panel A, row 2). Within the low CR group, ε4+ had reduced cortical thickness compared ε4- in the left hippocampus ($t(16)= 2.33$, $p<0.05$) (Figure 2, panel B, row 1) and trends in this direction for the left pars opercularis ($t(16)= 2.10$, $p=0.05$) (Figure 2, panel B, row 2), left inferior parietal ($t(16)= 1.80$, $p=0.09$) (Figure 2, panel B, row 3), and right insula ($t(16)= 2.01$, $p=0.06$) (Figure 2, panel B, row 4). T-tests revealed non-significant differences between ε4 groups within high and low CR in the right inferior parietal.

No statistically significant influences of CR2, or the interaction of CR2 and ε4 inheritance were observed in the remaining FPN, MTL/HC regions (See Table 13 (row A panel 2, rows B-C, row D panel 2, row E, row F panel B, row H) and Table14 (row B-C))

CR3 and Cortical Thickness Per Label. Main effects of CR3 were observed in 2 of the 12 regions, including the left pars triangularis ($F(1, 33)= 11.11$, $p<0.01$) (Table 18, panel A, row F) and right pars triangularis ($F(1, 33)=5 .05$, $p<0.05$) (Table 18, panel B, row F). In both regions, high CR3 was associated with greater cortical thickness than low CR3. Interaction effects of CR3 and ε4 inheritance were observed in 4 of the 12 regions, including the left rostral MFG ($F(1, 33)= 5.55$, $p<0.05$) (Table 18, panel A, row 1), left insula ($F(1, 33)= 6.37$, $p<0.05$) (Table 18, panel B, row I), right insula ($F(1, 33)= 4.84$, $p<0.05$) (Table 18, panel B, row I), and right PHG ($F(1, 33)= 4.25$, $p<0.05$) (Table 19, panel 2, row B).

Post hoc hierarchical regression analyses revealed that CR3 contributed to the model at Step 3 for the left pars triangularis ($R^2\Delta=0.23$, $p<0.01$) (Table 20, row B) and right pars triangularis ($R^2\Delta=0.10$, $p<0.05$) (Table 21, row A). The interaction of CR3 and

ε4 significantly predicted cortical thickness at Step 4 in the left rostral MFG ($R^2\Delta$=0.11, p<0.05) (Table 20, row A), right inferior parietal ($R^2\Delta$=0.11, p<0.05) (Table 21, row C), and right superior parietal ($R^2\Delta$=0.10, p<0.05) (Table 21, row D). Hierarchical regressions predicting bilateral insula and right PHG did not yield statistically significant contributions of CR3, ε4, or the interaction term (Table 21, row E).

Post hoc t-tests revealed a trend for greater cortical thickness in ε4+ compared to ε4- within the high CR3 group for the left rostral MFG (t(16)= -1.96, p=0.07) (Figure 3, panel 1, row A) and left insula (t(16)= -2.01, p=0.06) (Figure 3, panel 1, row C). Within the low CR3 group, there was a statistical trend for ε4- to have greater cortical thickness compared to ε4+ within the left insula (t(15)= 1.70, p=0.09) (Figure 3, panel 1, row C), right insula (t(15)= 2.10, p=0.05) (Figure 3, panel 1, row B), and right PHG (t(15)= 2.08, p=0.06) (Figure 3, panel 2, row B).

No statistically significant influences of CR3, or the interaction of CR3 and ε4 inheritance were observed in the remaining FPN, MTL/HC regions (see Table 18 (rows B-E; G-H) and Table 19 (rows A, C, and B, panel 1).

Vertex Analyses

The GLM per vertex analyses over the masked FPN and MTL regions did not yield statistically significant results after FDR correction for CR1, CR2, or CR3. This is not unexpected given the small sample size; therefore the presented analyses define areas of significance as p<0.05. Regions of significance were identified by location and number, as multiple distinct vertex regions can be located within the same label. Post-hoc analyses were conducted for each significant region identified in the vertex analyses,

including t-tests and hierarchical regression analysis predicting cortical thickness (Step 1=age, Step 2=ε4 inheritance, Step 3=CR, Step 4=CRxε4 interaction term).

CR1 and Cortical Thickness per Vertex. Figure 4 shows the GLM per vertex analysis for CR1 where $p<0.05$. Fourteen regions of significance from this analysis revealed that the correlation of CR1 and cortical thickness was greater for ε4+ than ε4-, including bilateral insula, bilateral superior parietal, bilateral inferior parietal, bilateral caudal ACC, right rostral MFG, and right PHG. Post hoc hierarchical regressions revealed that CR1 at Step 3 predicted right caudal ACC thickness (Table 23, row D), ($R^2\Delta$=0.14, β= 0.37, $p<0.05$), and indicated that those with high CR had greater cortical thickness than those with low CR. The interaction term of CR1 and ε4 significantly predicted cortical thickness in the left insula ($R^2\Delta$=0.26, β= 0.68, $p<0.01$) (Table 22, row A), left superior parietal ($R^2\Delta$=0.24, β= 0.49, $p<0.05$) (Table 22, row E), left inferior parietal, ($R^2\Delta$=0.25, β= 0.68, $p<0.01$) (Table 22, row C), left inferior parietal ($R^2\Delta$=0.30, β= 0.74, $p<0.01$) (Table 22, row D), left superior parietal ($R^2\Delta$= 0.35, β= 0.65, $p<0.01$) (Table 22, row E) left caudal ACC ($R^2\Delta$=0.17, β= 0.56, $p<0.01$) (Table 22, row F), right insula ($R^2\Delta$=0.18, β= 0.57, $p<0.05$) (Table 23, row A), right inferior parietal ($R^2\Delta$= 0.30, β= 0.74, $p<0.01$) (Table 23, row B), right superior parietal ($R^2\Delta$= 0.23, β= 0.64, $p<0.01$) (Table 23, row C), and right caudal ACC ($R^2\Delta$=0.19, β= 0.58, $p<0.01$) (Table 23, row D). Main and interaction effects of CR1, ε4, or CR1 x ε4 were non-significant in the right rostral MFG (Table 24, row A), right superior parietal (Table 24, row B), right superior parietal (Table 24, row C), right PHG (Table 24, row D).

Post hoc t-tests revealed that ε4+ had greater cortical thickness compared to ε4- within the high CR1 group in the right rostral MFG ($t(16)$= -2.42, $p<0.05$) (Figure 6,

graph 7) and a trend in the same direction in the left superior parietal ($t(16)= -1.84$, $p=0.09$) (Figure 5, graph 2). Within the low CR group, there were trends for ε4- showed greater cortical thickness compared to ε4+ in the left inferior parietal ($t(15)= 1.89$, $p=0.08$) (Figure 5, graph5), and left caudal ACC ($t(15)= 1.84$, $p=0.09$) (Figure 5, graph 6), and right caudal ACC ($t(15)= 2.07$, $p=0.56$) (Figure 7, graph 13). The pattern of cortical thickness results was mixed where thickness was different between ε4 carriers in the high CR1 group (ε4 carriers have greater cortical thickness than ε4 non-carriers), while other regions showed that cortical thickness differed between ε4 carriers in the low CR1 group (ε4 non-carriers have greater cortical thickness than ε4 carriers).

CR2 and Cortical Thickness per Vertex. Figure 8 shows the GLM per vertex analysis for CR2 where $p<0.05$. Twenty-one regions of statistical significance from this analysis indicated the correlation of CR2 and cortical thickness was greater for ε4+ than ε4- in bilateral rostral MFG, insula inferior parietal, superior parietal, left pars triangularis and caudal ACC, and right pars opercularis and PHG.

Post hoc hierarchical regressions revealed that CR2 significantly predicted cortical thickness at Step 3 in the left superior parietal ($R^2\Delta= 0.16$, $\beta= 0.40$, $p<0.05$) (Table 26, row C), left inferior parietal ($R^2\Delta= 0.16$, $\beta= 0.41$, $p<0.05$) (Table 26, row D), and right superior parietal ($R^2\Delta= 0.18$, $\beta= 0.42$, $p<0.05$) (Table 27, row E). The interaction of CR2 and ε4 significantly predicted cortical thickness at Step 4 in two regions in the left rostral MFG ($R^2\Delta= 0.23$, $\beta= 0.72$, $p<0.01$; Table 25, row A) ($R^2\Delta= 0.22$, $\beta= 0.70$, $p<0.01$; Table 25, row B), left pars triangularis ($R^2\Delta= 0.15$, $\beta= 0.58$, $p<0.05$) (Table 25, row C), left caudal ACC ($R^2\Delta= 0.21$, $\beta= 0.68$, $p<0.01$) (Table 25, row D), two regions in the left insula ($R^2\Delta= 0.15$, $\beta= 0.58$, $p<0.05$;Table 26, row A), ($R^2\Delta=$

0.29, β= 0.80, p<0.01; Table 26, row B), three regions in the two regions in the left inferior parietal (R^2Δ= 0.27, β= 0.76, p<0.01; Table 26, row C), (R^2Δ= 0.20, β= 0.66, p<0.01; Table 26, row D), two regions in the left superior parietal (R^2Δ= 0.24, β= 0.73, p<0.01; Table 26, row E), (R^2Δ= 0.29, β= 0.79, p<0.01; Table 26, row F), right pars opercularis (R^2Δ= 0.15, β= 0.58, p<0.05) (Table 28, row A), three regions in the right insula (R^2Δ= 0.20, β= 0.67, p<0.01; Table 27, row A), (R^2Δ= 0.15, β= 0.57, p<0.05; Table 27, row B), (R^2Δ= 0.23, β= 0.70, p<0.01; Table 27, row C), right inferior parietal (R^2Δ= 0.34, β= 0.87, p<0.01) (Table 27, row D), and two regions in the right superior parietal (R^2Δ= 0.32, β= 0.83, p<0.01;Table 27, row E), (R^2Δ= 0.19, β= 0.65, p<0.05) (Table 27, row F). Within the MTL/HC the interaction of CR2 and ε4 significantly predicted cortical thickness at Step 4 in two regions in the right PHG (R^2Δ= 0.16, β= 0.60, p<0.05; Table 28, row B) (R^2Δ= 0.14, β= 0.55, p<0.05; Table 28, row C).

Post hoc t-tests revealed greater cortical thickness in ε4+ compared to ε4- within the high CR2 group for two regions in the left rostral MFG (t(15)= -3.08, p<0.01; Figure 9, graph 1), (t(15)= -2.86, p<0.05; Figure 9, graph 4), two regions in the left insula (t(15)= -1.79, p=0.09; Figure 9, graph 5), (t(15)= -4.07, p<0.01; Figure 9, graph 6), two regions in the left superior parietal (t(15)= -1.96, p=0.068; Figure 10, graph 7), (t(15)= -1.95, p=0.07; Figure 10, graph 10), two regions in the right insula (t(15)= -1.91, p=0.07; Figure 11, graph 14), (t(15)= -2.57, p<0.05; Figure 11, graph 16), right inferior parietal (t(15)= -2.35, p<0.05) (Figure 11, graph 17), and two regions in the right superior parietal (t(15)= -2.56, p<0.05; Figure 11, graph 18), (t(15)= -2.85, p<0.05; Figure 12, graph 19).

T-tests revealed greater cortical thickness in ε4- compared to ε4+ within the low CR2 group for the left rostral MFG (t(16)=1.81, p=0.089) (Figure 9, graph 1), left pars

triangularis ($t(16)=3.04$, $p<0.01$) (Figure 9, graph 3), two regions in the left inferior parietal ($t(16)= 2.13$, $p<0.05$; Figure 10, graph 8), ($t(16)= 2.77$, $p<0.05$; Figure 10, graph 9), left superior parietal ($t(16)= 3.05$ $p<0.01$) (Figure 10, graph 7), right pars opercularis ($t(16)= 3.12$, $p<0.01$) (Figure 11, graph 15), right rostral MFG ($t(16)= 2.26$, $p<0.05$) (Figure 11, graph 12), two regions in the right insula ($t(16)= 1.90$, $p=0.08$; Figure 11, graph 13), ($t(16)= 2.23$, $p<0.05$; Figure 11, graph 16), and right superior parietal ($t(16)= 3.21$, $p<0.01$) (Figure 11, graph 18). The pattern of cortical thickness results was mixed where thickness was different between ε4 carriers in the high CR2 group (ε4 carriers have greater cortical thickness than ε4 non-carriers), while other regions showed that cortical thickness differed between ε4 carriers in the low CR2 group (ε4 non-carriers have greater cortical thickness than ε4 carriers).

CR3 and Cortical Thickness per Vertex. Figure 13 shows the GLM per vertex analysis for CR3 where $p<0.05$. Twenty-one regions of significance from this analysis indicated the correlation of CR3 and cortical thickness was greater for ε4+ than ε4- in bilateral rostral MFG, insula, superior parietal, inferior parietal, and left pars opercularis and PHG. Post hoc hierarchical regressions revealed that CR3 significantly predicted cortical thickness at Step 3 in the left insula ($R^2\Delta= 0.12$, $\beta= 0.37$, $p<0.05$) (Table 29, row C), left inferior parietal ($R^2\Delta= 0.12$, $\beta= 0.40$, $p<0.05$) (Table 30, row B), left superior parietal ($R^2\Delta= 0.18$, $\beta= 0.46$, $p<0.05$) (Table 30, row C), right inferior parietal ($R^2\Delta= 0.13$, $\beta= 0.39$, $p<0.05$) (Table 32, row B), and right superior parietal ($R^2\Delta= 0.19$, $\beta= 0.47$, $p<0.01$) (Table 32, row F). The interaction term of CR x ε4 significantly predicted cortical thickness in the left rostral MFG ($R^2\Delta= 0.27$, $\beta= 0.81$, $p<0.01$) (Table 29, row A), left pars opercularis ($R^2\Delta= 0.24$, $\beta= 0.77$, $p<0.01$) (Table 29, row B), two regions in the

left insula ($R^2\Delta$= 0.12, β= 0.55, p<0.05; Table 29, row C), ($R^2\Delta$= 0.12, β= 0.55, p<0.05; Table 29, row C), two regions in the left inferior parietal ($R^2\Delta$= 0.20, β= 0.69, p<0.01; Table 30, row A), ($R^2\Delta$= 0.13, β= 0.55, p<0.05; Table 30, row B), two regions in the left superior parietal ($R^2\Delta$= 0.16, β= 0.63, p<0.01; Table 30, row C), ($R^2\Delta$= 0.20, β= 0.70, p<0.01; Table 30, row D), two regions in the right rostral MFG ($R^2\Delta$= 0.16, β= 0.62, p<0.05; Table 31, row A), ($R^2\Delta$= 0.16, β= 0.62, p<0.05; Table 31, row B), right pars opercularis ($R^2\Delta$= 0.13, β= 0.57, p<0.05) (Table 31, row C), right insula ($R^2\Delta$= 0.30, β= 0.85, p<0.01) (Table 31, row D), right inferior parietal ($R^2\Delta$= 0.15, β= 0.61, p<0.05) (Table 32, row A), and four regions in the right superior parietal ($R^2\Delta$= 0.21, β= 0.72, p<0.01; Table 32, row C), ($R^2\Delta$= 0.16, β= 0.63, p<0.05; Table 32, row D), ($R^2\Delta$= 0.14, β= 0.59, p<0.05; Table 32, row E), ($R^2\Delta$= 0.14, β= 0.59, p<0.05; Table 32, row F).

Post hoc t-tests revealed greater cortical thickness in ε4+ compared to ε4- within the high CR3 group in the left rostral MFG (t(16)= -4.02, p<0.01) (Figure 14, graph 1), left pars opercularis (t(16)= -2.00, p=0.06) (Figure 14, graph 2), left insula (t(16)= -3.12, p<0.01) (Figure 14, graph 3), left insula (t(16)= -3.02, p<0.01) (Figure 14, graph 4), left superior parietal (t(16)= -4.02, p=0.089) (Figure 15, graph 6), left inferior parietal (t(16)= -2.12, p=0.05) (Figure 15, graph 7), right rostral MFG (t(16)= -1.79, p=0.093) (Figure 16, #11), right pars opercularis (t(16)= -2.32, p<0.05) (Figure 16, graph 14), right insula (t(16)= -2.73, p<0.05) Figure 16, graph 15), and right superior parietal (t(16)= -3.69, p<0.01) (Figure 17, #16). Within the low CR group, ε4- had greater cortical thickness than ε4+ in the left rostral MFG (t(15)= 2.20, p<0.05) (Figure 14, graph 1), left pars opercularis (t(15)= 1.85, p=0.09) (Figure 14, graph 2), left insula (t(15)= 2.81, p<0.05) (Figure 14, graph 3), left pars opercularis (CR3.5) (t(15)= 1.80, p=0.09), right insula

($t(15)= 2.68$, $p<0.05$) (Figure 16, graph 15), and right superior parietal ($t(15)= 2.09$, $p=0.05$) (Figure 17, graph 19). The pattern of cortical thickness results was mixed where thickness was different between ε4 carriers in the high CR3 group (ε4 carriers have greater cortical thickness than ε4 non-carriers), while other regions showed that cortical thickness differed between ε4 carriers in the low CR3 group (ε4 non-carriers have greater cortical thickness than ε4 carriers).

DISCUSSION

This study explored the complex relationship of genetic risk of Alzheimer's disease (AD) with lifetime protective factors known as cognitive reserve (CR) on both cognitive and neural integrity in healthy older adults. The current study adds to the literature by exploring three different CR proxies on cognitive functioning and cortical thickness. The proxies included education and verbal IQ (CR1) (Stern et al., 2005), education, occupation, and leisure activities (CR2) (Sole-Padulles et al., 2009), and a new CR composite comprised of education, occupation, leisure activities, and health factors (hip-waist ratio, blood pressure, and intake frequency of foods rich in vitamins B, D, E, and folates).

Regarding the neuropsychological data, it was hypothesized that ε4 carriers would have poorer cognitive performance in executive functioning but not in memory in this cognitively intact sample. It was further hypothesized that ε4 carriers with high CR would have better performance than ε4 carriers with low CR. Regarding individual CR measures, CR3 was predicted to show a stronger relationship to executive functioning (EF) performances than CR1 and CR2. The data partially supported the hypotheses. EF

was more strongly related to CR3 than CR1 and CR2. Interestingly, across all analyses on the FAS component within CR2 showed an interaction between CR and ε4, where ε4 carriers with high CR had better performance than ε4 non-carriers with high CR. The remainder of the analyses showed that CR alone was more predictive of cognitive performance than was the interaction of ε4 and CR. Contrary to the hypotheses, ε4 alone did not contribute to the findings.

Regarding cortical thickness, interaction effects between CR and ε4 were expected in FPN regions, such that ε4 carriers would have reduced cortical thickness in the low CR group. CR and ε4 inheritance were not expected to have a statistically significant effect on medial temporal cortical thickness (MTL) and hippocampal volume in this cognitively normal sample. It was further predicted that there would be more interaction effects of CR and ε4 inheritance in CR3 than CR1 and CR2. Consistent with these hypotheses, the interaction of ε4 and CR was most predictive of FPN thickness across all CR measures. Contrary to predictions, analyses did not show uniform direction of differences (e.g. some analyses showed ε4 carriers had greater cortical thickness than ε4 non-carriers within the high CR group; other analyses showed that ε4 non-carriers had greater cortical thickness than ε4 carriers within the low CR group).

Regarding the overlap of label and vertex cortical thickness analyses, the vertex analysis revealed more interaction effects than label analyses across all CR measures. The vertex analysis confirmed label analyses and revealed additional regions of significance. Between CR measures, CR2 and CR3 revealed more interaction effects (21 regions in both CR2 and CR3), compared to CR1 (14 regions). Across all CR measures, interactions of ε4 and CR were observed in bilateral insula, inferior parietal, superior

parietal, and right rostral MFG. In addition, CR2 and CR3 both showed interaction effects in bilateral rostral MFG and right pars opercularis. CR1 and CR2 both showed interaction effects in the right PHG. In addition, CR1 showed interaction effects in the caudal ACC. CR2 showed additional interactions in the left pars triangularis and left hippocampus. CR3 showed interactions in left pars opercularis and left PHG. Finally, contrary to predictions, ε4 inheritance alone was not predictive of cortical thickness in label or vertex analyses.

Our results demonstrated that ε4 inheritance and CR together impacted both cognitive functioning and cortical thickness. This interaction of risk and protective factors was particularly and consistently observed within FPN including bilateral insula, inferior parietal, superior parietal, and right rostral MFG. The influence of ε4 and CR was less evident in MTL/HC regions with the exception that the right PHG, which consistently exhibited this relationship across all CR proxies. Indeed, this interaction was more predictive of cortical thickness than when CR and ε4 were considered separately. The interaction of ε4 and CR was also observed within verbal fluency (CR2) and cognitive flexibility (CR3), however, CR alone predicted the majority of cognitive findings.

While the interaction of CR and ε4 was evident in both cortical thickness and cognitive functioning, the specific intervening role is mixed. Within analyses that demonstrated an interaction of CR and ε4, approximately half showed an "additive benefit mechanism" such that high CR for ε4-carriers was particularly beneficial (i.e. greater cortical thickness or better cognitive performance), while ε4 inheritance within those with low CR was non-contributory. An "additive detriment mechanism" was also

frequently observed whereby ε4 inheritance within low CR groups presented a larger disadvantage than either factor alone (i.e. reduced cortical thickness or lower cognitive performance) while no influence of ε4 inheritance within those with high CR was observed.

Cortical thickness findings revealed that approximately half of the interactions observed demonstrated the additive benefit mechanism (CR1: 2/5 interactions; CR2: 12/22 interactions) and the other half showed the additive detriment mechanism. Interestingly, CR3 showed more additive benefit mechanisms (CR3: 10/15 interactions) than additive detriment. Furthermore, neither mechanism was consistently associated with specific anatomical regions. For example, the left insula showed the additive benefit mechanism with CR2 and the additive detriment with CR3 analyses. In contrast, the cognitive findings revealed mostly main effects of CR (i.e., better cognitive performance in the high CR group). However, the additive benefit mechanism was observed in the one observed interaction effect of CR2 and verbal fluency.

The notion that ε4 carriers benefit more from protective factors more than non-carriers (i.e. the added benefit mechanism), may seem counter-intuitive. Nevertheless, the literature shows growing evidence that ε4 carriers show better responses to intervention than non-carriers (Arenaza-Urquijo et al., 2015; Bizzarro et al., 2005; Etnier et al., 2007; Evans et al., 2013; Pizzie et al., 2014; Smith et al., 2011). Exercise in ε4 carriers is associated with cognitive gains in executive functioning (Pizzie et al., 2014) and greater functional activation during a semantic memory task in several frontal regions (left MFG, superior frontal gyrus) and parietal (right insula, superior parietal, supramarginal, precuneus) regions (Smith et al., 2011). Furthermore, those at greatest genetic risk for

AD (ε4 homozygotes) showed more cognitive improvements in an exercise intervention than non-carriers and even ε4 heterozygotes (Etnier et al., 2007). In addition to exercise, the additive benefit mechanism was observed in a donepezil trial and showed that ε4 carriers with probable AD showed stable or improved cognitive performance compared to non-ε4 carriers (Bizzarro et al., 2005). Nicotine as a cholinergic agonist has also shown particular benefits with young ε4 carriers compared to non-ε4 carriers in executive functions (verbal fluency and decision making) (Marchant, King, Tabet, & Rusted, 2010) and medial frontal activation during a memory task (Evans et al., 2013).

The literature also supports the additive detriment mechanism. In particular, ε4 carriers with vascular risk factors such as hypertension, high BMI, and diabetes had worse cognitive performance in memory, attention, executive functions, and visuospatial abilities compared to non-carriers with cardiovascular risks (Bangen et al., 2013; Ravona-Springer et al., 2014). This relationship was evident even with subtle risks, such as pre-hypertensive blood pressure within ε4 carriers only (Oberlin et al., 2015). Neuroimaging shows that ε4-carriers have greater amyloid beta burden compared to non-carriers, though ε4-carriers who were sedentary had increased amyloid burden compared to sedentary non-ε4 carriers (Head et al., 2012). Finally, reduced entorhinal thickness in those with low CR had earlier cognitive decline than those with high CR. Unfortunately, this study did not specifically examine the association of genetic risk with CR (Soldan et al., 2015).

The current findings together with the presented literature indicate that genetic risk and CR have a synergistic effect that can dually increase or decrease risk factors associated with AD. Interestingly, many regions that evidenced interaction effects of CR and ε4 both in the current study (rostral MFG, superior parietal, inferior parietal), and in

the reviewed literature (frontotemporal, parietal, temporal, cingulate) (Arenaza-Urquijo et al., 2015; Evans et al., 2013; Smith et al., 2011; Soldan et al., 2015) are vulnerable to amyloid beta deposition in Alzheimer's disease (Klunk et al., 2004; Perrin, Fagan, & Holtzman, 2009). Therefore, the interaction of cortical thickness and ε4 in frontal and parietal regions may be indicative of altering underlying pathology in regions that would otherwise show reduced cortical thickness and amyloid-beta pathology.

Interestingly, ε4 alone did not demonstrate a significant relationship with cognitive functioning or cortical thickness in this cross-sectional sample of healthy elders, which is not consistent with the larger literature. A meta-analysis of 77 studies concluded that healthy elders who inherited the ε4 allele had poorer memory and executive functions than their non-ε4 carrying counterparts (Wisdom, Callahan, & Hawkins, 2011), though there is some evidence that age may mediate this relationship, such that the observed negative influence of ε4 on cognitive functioning were not observed in some studies until the 7th decade of life (Sapkota, Backman, & Dixon, 2017; Wisdom et al., 2011), which is slightly younger than the mean age of our current cohort and therefore cognitive decline mediated by ε4 inheritance may be observed later within our sample. Another study showed baseline differences in memory within ε4 carrying healthy elders. Over 4 years, memory, executive functions, and language, declined faster among ε4 carriers (Ganguli et al., 2014). Similarly, healthy ε4 carriers have shown reduced cortical thickness in MTL regions (Burggren et al., 2008) and tend to show accelerated cortical thinning over time compared to healthy non-carriers (Espeseth et al., 2008). There is some evidence that this effect may be dose-dependent as a large-scale study showed longitudinal cortical thinning in exclusively ε4 homozygotes (Crivello et

al., 2010). Given our small sample size and the subtle effects in both cognitive and cortical thickness, it is possible that we did not have statistical power to detect these effects if they exist. It is also possible that our sample is younger than some of these studies and therefore, may not show negative influences of ε4 on cognition at this early stage.

Regional specific associations were observed across all CR proxies in bilateral insula, inferior parietal, superior parietal, and right rostral middle frontal gyrus (MFG). Similar to the current results, parietal involvement in cognitive reserve is well documented in the literature (Fernandez-Cabello et al., 2016; Pena-Gomez et al., 2012; Stern et al., 2005). Unfortunately, very few studies were found that examined the relationship of CR in cortical thickness. Nevertheless, functional hyperactivation in parietal regions during cognitive tasks is well documented (Fernandez-Cabello et al., 2016; Pena-Gomez et al., 2012; Stern et al., 2005), suggesting a healthy compensatory process whereby additional neurons are recruited to maintain functioning due tissue or neuronal damage, consistent with STAC theories (Park & Reuter-Lorenz, 2009).

Specific to CR measurement, our study showed that CR1 did not show a significant relationship within any cognitive domain assessed. Within cortical thickness, CR1 did show specific relationships to the right anterior cingulate cortex (ACC) that were not observed in CR2 or CR3. CR and right ACC involvement is documented in the literature, particularly among studies that use verbal IQ and education proxies for CR (Arenaza-Urquijo et al., 2013; Ferreira et al., 2016; Stern et al., 2005; Vaque-Alcazar et al., 2016). Within those with high education, the ACC specifically has shown larger volume and more connectivity with the hippocampus and IFG during resting state, In

turn, this is associated with better performance in verbal fluency and delayed recall (Arenaza-Urquijo et al., 2013). As such, the ACC appears to play a role in communication with both frontoparietal network systems and hippocampal regions, and are associated with expected executive functions and memory performances. Therefore, Arenaza-Urquijo et al. (2013) shows that years of education bolsters ACC functioning, which improves both memory and executive functions, possibly through increased connectivity.

Within our cortical thickness findings, CR2 and CR3 were associated with greater frontal involvement than CR1. These CR2 and CR3 proxies differed with CR1 based on the inclusion of leisure activities. Other neuroimaging studies that included leisure activities in CR measurement also found an associated with frontal regions (Bartres-Faz et al., 2009; Bosch et al., 2010). Within healthy older adults, high CR was associated with greater grey matter volume and neuronal efficiency in a working memory task (Bartres-Faz et al., 2009). Within cognitively impaired samples, CR is associated with additional recruitment of frontal regions (Bosch et al., 2010). Moreover, individuals with sedentary lifestyles at midlife had reduced volume in middle frontal regions in later life (Rovio et al., 2010), suggesting an important role of an active lifestyle with frontal region integrity.

CR2 was the only CR proxy to show hippocampal involvement and an association with verbal memory. The observed interaction of ε4 and CR2 in the hippocampus evidenced the additive detrimental effect such that ε4 carriers with low CR (measured by education) showed significantly reduced hippocampal volume compared to low CR non-carriers. Similarly, healthy middle-aged participants with low CR have reduced hippocampal volumes, which are associated with reduced performance on a memory test;

this finding was not replicated within the high CR group (Vuoksimaa et al., 2013). Although education was the sole CR proxy in this study, there is some evidence that participating in challenging mental activities throughout the life is associated with slowed hippocampal atrophy over time (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008), though genetic risk was not considered in this study. Interestingly, CR2 was also associated with verbal memory factors, including the AVLT and Logical Memory, while CR3 was associated with executive functions, indicating that education, occupation, and leisure activities may show specific relationships to memory and HC/MTL pathology.

Similarly, CR3 was specifically associated with executive functioning and inferior frontal gyrus (IFG) thickness (i.e. pars triangularis, pars opercularis). Health factors (i.e. hip waist ratio, blood pressure, and nutrition) in CR3 separated this proxy from CR1 and CR3. Statistically, CR3 was more heterogeneous than CR1 and CR2 due to the inclusion of additional variables. However, hip-waist ratio showed reduced loading on this factor than the other variables and therefore, it is possible that the results may differ if the variables included in CR3 variables had similarly high loadings. Future work will investigate these relationships after removing this variable. Nevertheless, consistent with the inclusion of health variables, vascular risk factors such as hypertension and obesity in midlife have been associated with a decline in executive functions later in life, including cognitive flexibility, reasoning, and processing speed (de Frias, Schaie, & Willis, 2014; Debette, Seshadri, Beiser, Au, & Himali, 2011; Yaffe et al., 2014). Indeed, executive functions, but not memory, improved in a 2-year intervention of healthy older adults that targeted diet, exercise, and monitored vascular risks (Ngandu et al., 2015). IFG cortical thickness compliments the executive functioning findings in this study. Similarly, fitness

is associated with greater IFG tissue density (Gordon et al., 2008). Interestingly, this region was also associated with education in the same study. Unfortunately, education and aerobic fitness were considered separately and therefore there were no analyses that further explored the relationship of fitness and education in the IFG. Furthermore, in a study of cognitively healthy individuals with elevated BMI and blood pressure, the IFG showed over-activations during a verbal memory retrieval task (Braskie, Small, & Bookheimer, 2010). Interpretation of the latter finding is confounded given that the IFG findings took place during a memory retrieval task.

The current study shows that the interaction of ε4 and CR is particularly important in cortical thickness and to a lesser degree, cognitive functioning in healthy elders. The study also showed that comprehensive proxies of CR are more sensitive to both cognitive and cortical thickness findings. Indeed, education and verbal IQ alone was predictive of fewer and smaller regions within cortical thickness. Including leisure activities to CR showed memory and hippocampal involvement. While CR2 was associated with FPN regions, the HC and memory associations were inconsistent with the initial hypothesis, though still supported by the literature. CR3 findings supported the initial hypothesis and showed that adding health factors to the CR composite was associated with executive functions and cortical thickness in frontal regions.

This study adds to our understanding of genetic risk and CR by exploring the relationship on both behavior and cortical thickness. Exploration of CR measurement further elucidated the impact of specific proxies with results. Our findings suggest that including leisure activities and health factors is beneficial to a well-rounded understanding of cognitive and neural changes associated with CR. Furthermore, leisure

activities and health factors are modifiable, and therefore the current results have important clinical implications. The current results show that CR can buffer cognitive and neural changes associated with genetic risk of developing AD. Therefore, promotion of healthy lifestyle activities and vascular functioning may offset some risk to developing AD and delay cognitive decline.

Results of the current study show mixed support for the executive decline theory of cognitive aging (Dempster, 1992; Parkin, 1997). Findings from CR3 were consistent with this hypothesis, such that several interactions of CR3 and ε4 inheritance were observed in executive functions and frontal regions. However, CR2 findings indicated memory functions and left hippocampal volume with additional frontal and parietal region findings. Interestingly, PHG findings were observed in all three CR factors. Therefore, although CR exhibited relationships of EF and frontal regions, the current findings implicate that CR is also associated with memory and MTL/HC processes even in a cognitively healthy and relatively young older adult sample.

The functional neuroimaging literature demonstrates both increased BOLD signal (Braskie et al., 2010; Smith et al., 2011) and reduced activation (Bartres-Faz & Arenaza-Urquijo, 2011) in high CR, which has been related to improved neural efficiency. Increased activation is thought to represent STAC theories, where increased activation is a healthy coping strategy due to underlying neuropathology (Park & Reuter-Lorenz, 2009). Integrating CR theory with STAC, over-activations observed in the literature likely represent neural compensation, whereby a change in typical processing has occurred and the brain is actively coping by recruiting different regions, neural networks, and strategies to overcome the disruption (Stern, 2009). Improved neural efficiency may

better related to neural reserve, another CR process that describes individual differences at baseline with regard to speed and capacity of the system and how those with more efficient neural networks may better cope with underlying pathology. The current study cannot directly address these issues, although the finding of increased cortical thickness in high CR may be indicative of greater neuroplasticity in high CR.

The study has several limitations. First, the sample characteristics are not ideal for examining CR. Our sample was small, which limited statistical power and may have resulted in Type II errors. Second, our sample was relatively young, predominantly Caucasian, and highly educated. It is possible that our sample was skewed to having high CR at baseline and therefore our low CR findings may be different if our sample characteristics included those with low education and was more racially diverse. The cross-sectional design is also not ideal for this topic. It would be highly beneficial to understand the influence of different CR proxies with genetic risk over time. Finally, the current study examined FPN, MTL, and HC regions specifically. Therefore it is possible that additional regions are associated with CR and ε4 that were not explored within the current study. Future studies should focus on a longitudinal design with a more inclusive sample to understand the entire CR spectrum. Additionally, future studies should also explore underlying mechanisms of cortical thickness and ε4 by including functional data and amyloid imaging to ascertain the in-vivo mechanism of action.

In conclusion, within a sample of healthy elders, CR showed protective benefits within cognitive functioning and cortical thickness. The relationship of CR and ε4 inheritance was particularly influential to cortical thickness in both frontoparietal regions and medial temporal/hippocampal regions. Some regions showed that high CR was

particularly beneficial to ε4 carriers, while other regions showed that low CR was particularly detrimental for those with ε4 inheritance. These findings are applicable to clinical practice to maximize cognitive and neurological functioning in healthy elders. This study highlights the need to understand lifetime and behavioral influences on risk for Alzheimer's disease.

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Table 1

Sample Demographics (mean (±SD))

Variable	ε4+ (N=16)	ε4- (N=19)	*p*-value
Age	67.8 (10.0)	65.0 (8.3)	0.28
Male/Female	5/11	10/9	0.31
Education	15.74 (2.26)	15.38 (2.13)	0.63
MMSE	29.26 (1.15)	29.63 (0.81)	0.30

Notes: ε4+ = apolipoprotein-E ε4 allele carrier; ε4-=apolipoprotein-E ε4 allele non-carrier; MMSE= Mini Mental State Exam

Table 2

PCA (Principle Components Analysis) Results of CR1, CR2, and CR3 Factors

Variable	CR1	CR2	CR3
NAART	0.61	0.58	0.26
Education (Years)	0.61		
7-point Education/Occupation Scale		0.83	
Cognitive, Physical, and Social Leisure Activities		0.84	
9-point Education/Occupation Scale			0.53
Physical, Cognitive, Social, Cultural, Work/Leadership Leisure Activities			0.47
Hip-Waist Ratio			0.18
Systolic Blood Pressure			0.74
Diastolic Blood Pressure			0.77
Nutrition Survey			0.72

Notes: NAART=North American Adult Reading Test

Table 3

Results of the Neuropsychology Assessment PCA

	Component						
Subtest	*1: RAVLT*	*2: COWA*	*3: TMT/SDMT*	*4: WCST*	*5: LogMem*	*6: DSF/DSB*	*7: DSS/DigCopy*
LogMem_IR	0.135	0.097	0.091	0.002	**0.958**	-0.033	0.048
LogMem_DR	0.214	0.036	0.066	0.246	**0.921**	0.007	0.076
DigSpan_Fwd	-0.002	0.000	0.198	0.004	-0.188	**0.808**	-0.189
DigSpan_Bwd	0.070	0.148	-0.121	0.065	0.138	**0.815**	0.182
RAVLTTrials1_5	**0.827**	0.213	0.281	0.136	0.233	0.099	-0.057
RAVLT_IR	**0.900**	0.015	0.136	0.219	0.133	-0.026	0.127
RAVLT_DR	**0.855**	0.161	0.198	0.174	0.231	0.097	0.128
COWA_F	0.066	**0.871**	-0.076	0.167	0.030	0.076	0.236
COWA_A	0.138	**0.774**	0.182	-0.062	0.144	0.349	0.046
COWA_S	0.208	**0.718**	0.176	0.234	0.166	-0.023	0.061
SDMT	0.283	0.199	**0.782**	0.023	0.320	0.012	-0.082
TrailsA_Time	-0.200	0.178	**-0.821**	-0.076	0.020	-0.056	0.030
TrailsB_Time	-0.142	-0.362	**-0.751**	-0.042	-0.087	-0.129	-0.171
WCST_TotalErrors	-0.153	-0.379	-0.147	**-0.811**	-0.205	0.003	0.049
WCST_Perseverative	-0.208	-0.410	-0.088	**-0.795**	-0.201	0.022	-0.108
WCST_Conceptual	0.141	-0.259	-0.066	**0.837**	-0.006	0.089	0.058
DigitCopy	0.078	0.118	-0.260	0.144	0.024	-0.251	**0.810**
DigSpan_Seq	0.025	0.039	0.343	-0.104	0.071	0.281	**0.783**

Notes. LogMem=WMS-III Logical Memory, IR=Immediate Recall, DR=Delayed Recall, DigSpan=WMS-IV Digits; Fwd=Forward, Bwd=Backward, Seq=Sequencing, WCST=Wisconsin Card Sorting Test, SDMT=Symbol Digit Modality Test, Loadings ≥ |.40| are in **bold**

Table 4

ANCOVA Results for CR1 and Cognitive Factors

	F	$\eta_p 2$	*p*
1. AVLT			
ε4	1.28	0.04	0.27
CR1	2.63	0.08	0.12
ε4 x CR1	0.45	0.01	0.71
Age (Covariate)	1.97	0.06	0.17
2. FAS			
ε4	0.70	0.02	0.41
CR1	0.08	0.00	0.78
ε4 x CR1	0.01	0.00	0.92
Age (Covariate)	0.14	0.01	0.71
3. TMT/SDMT			
ε4	0.30	0.01	0.59
CR1	4.00+	0.12	0.06
ε4 x CR1	0.18	0.01	0.68
Age (Covariate)	8.60**	0.22	0.01
4. WCST			
ε4	0.02	0.00	0.89
CR1	0.50	0.02	0.49
ε4 x CR1	0.68	0.02	0.42
Age (Covariate)	0.62	0.02	0.44
5. Log Mem			
ε4	0.03	0.00	0.86
CR1	0.04	0.00	0.85
ε4 x CR1	0.30	0.01	0.61
Age (Covariate)	2.10	0.06	0.16
6. DSF/DSB			
ε4	2.01	0.06	0.17
CR1	0.02	0.00	0.88
ε4 x CR1	2.51	0.08	0.12
Age (Covariate)	1.42	0.05	0.24
7. DSS/Digit Copy			
ε4	0.94	0.03	0.34
CR1	0.21	0.01	0.65
ε4 x CR1	0.01	0.00	0.94
Age (Covariate)	0.69	0.02	0.41

Notes: +p<0.10, * p<0.05, **p<0.01; AVLT= Rey Auditory Verbal Learning Test; FAS=Controlled Oral Word Association Test; TMT= Trail Making Test; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test; DSF=Digit Span Forward; DSB= Digit Span Backward; DSS= Digit Span Sequencing

Table 5

Post Hoc Hierarchical Regression Predicting TMT/SDMT Factor from CR1 and ε4 Inheritance

	Model 1			**Model 2**			**Model 3**			**Model 4**		
Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
Age	-0.05	0.02	-0.45**	-0.05	0.03	-0.44**	-0.05	0.02	-0.45**	-0.05	0.02	-0.44**
ε4				-0.13	0.31	-0.06	-0.17	0.30	-0.09	-0.17	0.30	-0.09
CR1							0.60	0.29	0.31*	0.45	0.34	0.24
ε4 x CR1										0.21	0.26	0.15
R^2		0.20			0.21			0.30			0.32	
F		8.47**			4.20*			4.51*			3.52*	
$R^2 \Delta$					1.00			0.10			0.02	
F Δ					0.15			4.26*			0.69	

Notes: *p<0.05, **p<0.01

Table 6

ANCOVA Results for CR2 and Cognitive Factors

	F	$\eta_p 2$	*p*
1. AVLT			
ε4	0.55	0.02	0.47
CR2	4.21*	0.12	0.05
ε4 x CR2	0.46	0.02	0.50
Age (Covariate)	2.79	0.09	0.11
2. FAS			
ε4	0.68	0.02	0.41
CR2	0.47	0.02	0.50
ε4 x CR2	7.22*	0.19	0.01
Age (Covariate)	0.08	0.00	0.79
3. TMT/SDMT			
ε4	0.33	0.01	0.57
CR2	2.09	0.07	0.16
ε4 x CR2	0.62	0.02	0.44
Age (Covariate)	7.89*	0.21	0.01
4. WCST			
ε4	0.01	0.00	0.91
CR2	0.15	0.01	0.70
ε4 x CR2	2.20	0.07	0.15
Age (Covariate)	0.53	0.02	0.47
5. Log Mem			
ε4	0.02	0.00	0.89
CR2	6.41*	0.18	0.02
ε4 x CR2	0.03	0.00	0.86
Age (Covariate)	2.94	0.09	0.10
6. DSF/DSB			
ε4	1.52	0.05	0.23
CR2	0.58	0.02	0.45
ε4 x CR2	0.03	0.00	0.86
Age (Covariate)	1.18	0.04	0.29
7. DSS/Dig Copy			
ε4	0.75	0.02	0.39
CR2	1.77	0.06	0.19
ε4 x CR2	0.71	0.02	0.41
Age (Covariate)	0.72	0.02	0.40

Notes: *$p<0.05$, **$p<0.01$; AVLT= Rey Auditory Verbal Learning Test; FAS=Controlled Oral Word Association Test; TMT= Trail Making Test; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test; DSF=Digit Span Forward; DSB= Digit Span Backward; DSS= Digit Span Sequencing

Table 7:

Post Hoc Hierarchical Regression Predicting Cognitive Factors from CR2 and ε4 Inheritance

		Model 1			Model 2			Model 3			Model 4		
		B	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. AVLT	Age	-0.03	0.02	-0.22	-0.03	0.02	-0.25	-0.03	0.02	-0.27	-0.03	0.02	-0.27
	ε4				0.33	0.34	0.17	0.24	0.33	0.12	0.24	0.33	0.12
	CR2							0.68	0.32	0.35*	0.74	0.37	0.37+
	ε4 x CR2										-0.07	0.25	-0.06
	R^2		0.05			0.08			0.20			0.20	
	F		1.73			1.34			2.51-			1.85	
	$R^2 \Delta$					0.03			0.12			0.00	
	F Δ					0.96			4.54*			0.09	
B. FAS	Age	-0.01	0.02	-0.05	-0.01	0.02	-0.07	-0.01	0.02	-0.07	-0.01	0.02	-0.09
	ε4				0.30	0.36	0.15	0.28	0.36	0.14	0.31	0.35	0.15
	CR2							0.16	0.36	0.08	-0.21	0.39	-0.10
	ε4 x CR2										0.51	0.27	0.38+
	R^2		0.00			0.02			0.03			0.14	
	F		0.07			0.39			0.32			1.20	
	$R^2 \Delta$					0.03			0.01			0.11	
	F Δ					0.71			0.19			3.770-	
C. TMT/SDMT	Age	-0.05	0.02	-0.45**	-0.05	0.02	-0.44**	-0.05	0.02	-0.45**	-0.05	0.02	-0.46**
	ε4				-0.12	0.31	-0.06	-0.18	0.31	-0.09	-0.16	0.31	-0.08
	CR2							0.42	0.30	0.22	0.24	0.34	0.13
	ε4 x CR2										0.25	0.23	0.19
	R^2		0.20			0.21			0.26			0.28	
	F		8.47**			4.20*			3.53*			2.96*	
	$R^2 \Delta$					0.00			0.05			0.03	
	F Δ					0.15			1.95			1.19	
D. Log Mem	Age	-0.03	0.02	-0.26	-0.03	0.02	-0.26	-0.03	0.02	-0.28	-0.03	0.02	-0.28
	ε4				0.06	0.34	0.03	-0.05	0.32	-0.02	-0.05	0.32	-0.02
	CR2							0.80	0.31	0.41*	0.79	0.36	0.41*
	ε4 x CR2										0.01	0.24	0.01
	R^2		0.07			0.07			0.23			0.23	
	F		2.29			1.13			3.08*			2.23+	
	$R^2 \Delta$					0.00			0.16			0.00	
	F Δ					0.03			6.58*			0.00	

Notes: +p<0.10, * p<0.05, **p<0.01; FAS=Controlled Oral Word Association Test; TMT= Trail Making Test; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test; DSF=Digit Span Forward; DSB= Digit Span Backward; DSS= Digit Span Sequencing

Table 8

ANCOVA Results for CR3 and Cognitive Factors

	F	$\eta_p 2$	*p*
1. AVLT			
ε4	0.75	0.02	0.39
CR3	0.07	0.00	0.80
ε4 x CR3	0.70	0.02	0.41
Age (Covariate)	1.41	0.04	0.26
2. FAS			
ε4	0.58	0.02	0.45
CR3	0.02	0.00	0.90
ε4 x CR3	0.34	0.01	0.57
Age (Covariate)	0.08	0.00	0.78
3. TMT/SDMT			
ε4	0.60	0.02	0.46
CR3	4.68*	0.14	0.04
ε4 x CR3	0.43	0.01	0.52
Age (Covariate)	3.86+	0.11	0.06
4. WCST			
ε4	0.23	0.01	0.63
CR3	8.77*	0.23	0.01
ε4 x CR3	0.08	0.00	0.77
Age (Covariate)	3.30+	0.10	0.08
5. Log Mem			
ε4	0.01	0.00	0.94
CR3	0.71	0.02	0.41
ε4 x CR3	0.35	0.01	0.56
Age (Covariate)	1.36	0.04	0.25
6. DSF/DSB			
ε4	1.59	0.05	0.22
CR3	0.22	0.01	0.65
ε4 x CR3	0.04	0.00	0.84
Age (Covariate)	1.4	0.04	0.25
7. DSS/Dig Copy			
ε4	0.75	0.02	0.40
CR3	0.5	0.02	0.49
ε4 x CR3	1.30	0.04	0.26
Age (Covariate)	0.22	0.01	0.65

Notes: +p<0.10, *p<0.05, **p<0.01; FAS=Controlled Oral Word Association Test; TMT= Trail Making Test; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test; DSF=Digit Span Forward; DSB= Digit Span Backward; DSS= Digit Span Sequencing

Table 9

Post Hoc Hierarchical Regression Predicting Cognitive Factors from CR3 and ε4 Inheritance

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. TMT/SDMT	Age	-0.05	0.02	-0.45**	-0.05	0.02	-0.44**	-0.04	0.02	-0.33*	-0.03	0.02	-0.30+
	ε4				-0.12	0.31	-0.06	-0.21	0.30	-0.11	-0.18	0.30	-0.09
	CR3							0.65	0.31	0.34*	0.47	0.35	0.24
	ε4 x CR3										0.25	0.23	0.19
	R^2		0.20			0.21			0.31			0.33	
	F		8.47**			4.20*			4.60**			3.75*	
	$R^2 \Delta$					0.00			0.10			0.02	
	F Δ					0.15			4.48*			1.15	
B. WCST	Age	0.02	0.02	0.15	0.02	0.02	0.15	0.04	0.02	0.32+	0.03	0.02	0.26
	ε4				-0.02	0.35	-0.01	-0.16	0.32	-0.08	-0.23	0.30	-0.12
	CR3							1.01	0.33	0.51**	1.39	0.35	0.70**
	ε4 x CR3										-0.52	0.23	-0.39*
	R^2		0.02			0.02			0.25			0.36	
	F		0.74			0.36			3.44*			4.13**	
	$R^2 \Delta$					0.00			0.23			0.11	
	F Δ					0.00			9.41**			4.91*	

Notes: +p<0.10, *p<0.05, **p<0.01; TMT= Trail Making Test; SDMT=Symbol Digit Modality Test; WCST=Wisconsin Card Sorting Test

Table 10

CR1 FPN Label Thickness ANCOVA Results

	1. Left Hemisphere				2. Right Hemisphere			
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. Rostral MFG	ε4	0.39	0.01	0.54	ε4	0.70	0.02	0.41
	CR1	0.22	0.01	0.64	CR1	0.04	0.00	0.84
	ε4 x CR1	0.01	0.00	0.93	ε4 x CR1	2.13	0.07	0.16
	Age (Covariate)	1.74	0.06	0.20	Age (Covariate)	0.84	0.03	0.37
B. Caudal ACC	ε4	0.19	0.01	0.67	ε4	0.81	0.03	0.38
	CR1	0.25	0.01	0.62	CR1	4.45*	0.13	0.04
	ε4 x CR1	0.53	0.02	0.47	ε4 x CR1	0.06	0.00	0.82
	Age (Covariate)	1.48	0.05	0.23	Age (Covariate)	0.14	0.01	0.71
C. Rostral ACC	ε4	0.02	0.00	0.89	ε4	0.01	0.00	0.94
	CR1	0.03	0.00	0.86	CR1	0.00	0.00	0.99
	ε4 x CR1	0.56	0.02	0.46	ε4 x CR1	0.98	0.03	0.33
	Age (Covariate)	1.11	0.04	0.30	Age (Covariate)	0.66	0.02	0.42
D. Pars Opercularis	ε4	0.34	0.01	0.57	ε4	0.01	0.00	0.93
	CR1	0.09	0.00	0.77	CR1	0.23	0.01	0.64
	ε4 x CR1	0.10	0.00	0.75	ε4 x CR1	1.92	0.06	0.18
	Age (Covariate)	3.78+	0.11	0.06	Age (Covariate)	6.17*	0.17	0.02
E. Pars Orbitalis	ε4	0.93	0.03	0.34	ε4	0.74	0.02	0.40
	CR1	0.53	0.02	0.47	CR1	0.57	0.02	0.46
	ε4 x CR1	0.56	0.02	0.46	ε4 x CR1	0.61	0.02	0.44
	Age (Covariate)	0.68	0.02	0.42	Age (Covariate)	11.77**	0.28	0.00
F. Pars Triangularis	ε4	0.67	0.02	0.42	ε4	1.05	0.03	0.31
	CR1	0.00	0.00	0.98	CR1	0.36	0.01	0.55
	ε4 x CR1	0.48	0.02	0.49	ε4 x CR1	0.06	0.00	0.81
	Age (Covariate)	0.66	0.02	0.42	Age (Covariate)	7.01*	0.19	0.01
G. Inferior Parietal	ε4	0.01	0.00	0.94	ε4	0.07	0.00	0.80
	CR1	0.00	0.00	0.97	CR1	0.01	0.00	0.93
	ε4 x CR1	0.93	0.03	0.34	ε4 x CR1	0.09	0.00	0.77
	Age (Covariate)	6.84*	0.19	0.01	Age (Covariate)	7.70*	0.20	0.01
H. Superior Parietal	ε4	1.05	0.03	0.31	ε4	0.71	0.02	0.41
	CR1	0.07	0.00	0.79	CR1	0.24	0.01	0.63
	ε4 x CR1	1.04	0.03	0.32	ε4 x CR1	0.33	0.01	0.57
	Age (Covariate)	6.72*	0.18	0.02	Age (Covariate)	4.75*	0.14	0.04
I. Insula	ε4	0.02	0.00	0.88	ε4	0.01	0.00	0.92
	CR1	0.01	0.00	0.91	CR1	0.37	0.01	0.55
	ε4 x CR1	1.30	0.04	0.26	ε4 x CR1	0.29	0.01	0.59
	Age (Covariate)	1.88	0.06	0.18	Age (Covariate)	3.55+	0.11	0.07

Notes: +p<0.10, *p<0.05, **p<0.01; FPN=Fronto-Parietal Network; MFG= Middle Frontal Gyrus; ACC= Anterior Cingulate Cortex

Table 11

CR1 Post Hoc Hierarchical Regression Predicting Right Caudal ACC Label Thickness

		Model 1			**Model 2**			**Model 3**			**Model 4**		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
RH Caudal ACC	Age	0.00	0.01	-0.02	0.00	0.01	-0.05	0.00	0.00	-0.07	0.00	0.00	-0.05
	ε4				0.09	0.09	0.18	0.07	0.08	0.15	0.07	0.08	0.15
	CR1							0.17	0.08	0.36*	0.13	0.09	0.27
	ε4 x CR1										0.07	0.07	0.18
	R^2		0.00			0.03			0.16			0.18	
	F		0.02			0.54			1.98			1.69	
	$R^2 \Delta$					0.03			0.13			0.02	
	F Δ					1.05			4.73*			0.86	

Notes: *p<0.05; RH=Right Hemisphere; ACC=Anterior Cingulate Cortex

Table 12

CR1 MTL/HC Label Thickness ANCOVA Results

		Left Hemisphere				Right Hemisphere		
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. HC	ε4	0.16	0.01	0.70	ε4	1.99	0.06	0.17
	CR1	0.12	0.00	0.73	CR1	0.22	0.01	0.65
	ε4 x CR1	0.24	0.01	0.63	ε4 x CR1	0.24	0.01	0.63
	Age (Covariate)	2.88	0.09	0.10	Age (Covariate)	1.68	0.05	0.21
B. PHG	ε4	0.82	0.03	0.37	ε4	0.01	0.00	0.91
	CR1	1.867	0.06	0.18	CR1	0.11	0.00	0.75
	ε4 x CR1	0.06	0.00	0.8	ε4 x CR1	0.02	0.00	0.89
	Age (Covariate)	0.91	0.03	0.35	Age (Covariate)	6.55*	0.18	0.02
C. Entorhinal	ε4	1.16	0.04	0.29	ε4	0.58	0.02	0.45
	CR1	0.34	0.01	0.57	CR1	0.00	0.00	0.96
	ε4 x CR1	0.05	0.00	0.83	ε4 x CR1	1.18	0.04	0.29
	Age (Covariate)	2.15	0.07	0.15	Age (Covariate)	3.96+	0.12	0.06

Notes: +p<0.10, * p<0.05, **p<0.01; MTL=Medial Temporal Lobe; HC= Hippocampus; PHG= Parahippocampal Gyrus

Table 13

CR2 FPN Label Thickness ANCOVA Results

	1. Left Hemisphere				2. Right Hemisphere			
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. Rostral MFG	ε4	0.36	0.01	0.55	ε4	0.86	0.03	0.36
	CR2	1.70	0.05	0.20	CR2	0.27	0.01	0.61
	ε4 x CR2	8.70**	0.23	0.01	ε4 x CR2	1.32	0.04	0.26
	Age (Covariate)	1.84	0.06	0.19	Age (Covariate)	0.59	0.02	0.45
B. Caudal ACC	ε4	0.15	0.01	0.70	ε4	0.3	0.03	0.94
	CR2	0.02	0.00	0.88	CR2	.01	0.00	0.91
	ε4 x CR2	0.09	0.00	0.77	ε4 x CR2	0.01	0.00	0.92
	Age (Covariate)	1.46	0.05	0.24	Age (Covariate)	0.09	0.00	0.77
C. Rostral ACC	ε4	0.01	0.00	0.94	ε4	0.01	0.00	0.91
	CR2	0.36	0.01	0.55	CR2	0.24	0.01	0.63
	ε4 x CR2	1.22	0.04	0.28	ε4 x CR2	0.09	0.00	0.76
	Age (Covariate)	1.35	0.04	0.25	Age (Covariate)	0.67	0.02	0.42
D. Pars Opercularis	ε4	0.58	0.02	0.45	ε4	0.04	0.00	0.84
	CR2	0.82	0.03	0.37	CR2	0.09	0.00	0.77
	ε4 x CR2	6.61*	0.18	0.02	ε4 x CR2	1.76	0.06	0.19
	Age (Covariate)	4.07+	0.12	0.05	Age (Covariate)	5.98*	0.17	0.02
E. Pars Orbitalis	ε4	0.71	0.02	0.41	ε4	0.52	0.02	0.48
	CR2	1.42	0.05	0.24	CR2	0.85	0.03	0.36
	ε4 x CR2	0.00	0.00	0.98	ε4 x CR2	1.86	0.06	0.18
	Age (Covariate)	0.79	0.03	0.38	Age (Covariate)	11.87**	0.28	0.00
F. Pars Triangularis	ε4	0.42	0.01	0.52	ε4	0.85	0.03	0.36
	CR2	3.580+	0.11	0.07	CR2	.07	0.00	0.79
	ε4 x CR2	5.509*	0.16	0.03	ε4 x CR2	0.01	0.00	0.92
	Age (Covariate)	0.749	0.03	0.39	Age (Covariate)	6.727*	0.18	0.02
G. Inferior Parietal	ε4	0.08	0.00	0.78	ε4	0.02	0.00	0.89
	CR2	3.50+	0.11	0.07	CR2	1.58	0.05	0.22
	ε4 x CR2	4.89*	0.14	0.04	ε4 x CR2	4.38*	0.13	0.05
	Age (Covariate)	7.82**	0.21	0.01	Age (Covariate)	8.48**	0.22	0.01
H. Superior Parietal	ε4	1.00	0.03	0.33	ε4	0.46	0.02	0.50
	CR2	0.27	0.01	0.61	CR2	2.21	0.07	0.15
	ε4 x CR2	2.71	0.08	0.11	ε4 x CR2	2.78	0.09	0.11
	Age (Covariate)	6.49*	0.18	0.02	Age (Covariate)	5.17*	0.15	0.03
I. Insula	ε4	0.05	2.00	0.82	ε4	0.02	0.00	0.88
	CR2	0.05	0.00	0.82	CR2	0.51	0.02	0.48
	ε4 x CR2	5.02*	0.14	0.03	ε4 x CR2	5.31*	0.15	0.03
	Age (Covariate)	1.56	0.05	0.22	Age (Covariate)	3.59+	0.11	0.07

Notes: +p<0.10, *p<0.05, **p<0.01; FPN=Fronto-Parietal Network MFG= Middle Frontal Gyrus; ACC= Anterior Cingulate Cortex

Table 14

CR2 MTL/HC Label Thickness ANCOVA Results

	1. Left Hemisphere				2. Right Hemisphere			
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. HC	ε4	0.19	0.01	0.66	ε4	2.03	0.06	0.16
	CR2	0.04	0.00	0.85	CR2	0.01	0.00	0.93
	ε4 x CR2	5.77*	0.16	0.02	ε4 x CR2	3.42+	0.10	0.07
	Age (Covariate)	2.86	0.09	0.10	Age (Covariate)	1.49	0.05	0.23
B. PHG	ε4	0.43	0.01	0.52	ε4	0.03	0.00	0.86
	CR2	0.68	0.02	0.42	CR2	0.13	0.00	0.73
	ε4 x CR2	0.00	0.00	0.98	ε4 x CR2	0.90	0.03	0.35
	Age (Covariate)	1.06	0.03	0.31	Age (Covariate)	6.49*	0.18	0.02
C. Entorhinal	ε4	1.02	0.03	0.32	ε4	0.57	0.02	0.46
	CR2	0.03	0.00	0.87	CR2	0.03	0.00	0.86
	ε4 x CR2	0.89	0.03	0.35	ε4 x CR2	1.36	0.04	0.25
	Age (Covariate)	2.08	0.07	0.16	Age (Covariate)	3.73+	0.11	0.06

Notes: +p<0.10, *p<0.05, **p<0.01; MTL=Medial Temporal Lobe; HC= Hippocampus; PHG= Parahippocampal Gyrus

Table 15

CR2 Post Hoc Hierarchical Regression Analyses Predicting Frontal Label Thickness

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. LH Rostral MFG	Age	0.00	0.00	-0.21	0.00	0.00	-0.23	0.00	0.00	-0.24	0.00	0.00	-0.26
	ε4				0.03	0.05	0.12	0.03	0.05	0.10	0.03	0.04	0.12
	CR2							0.05	0.05	0.17	-0.02	0.05	-0.06
	ε4 x CR2										0.09	0.03	0.47*
	R^2		0.05			0.06			0.09			0.26	
	F		1.59			1.02			0.99			2.62+	
	$R^2\Delta$					0.01			0.03			0.17	
	F Δ					0.47			0.93			6.95*	
B. LH Pars Opercularis	Age	-0.01	0.00	-0.35*	0.00	0.00	-0.33+	0.00	0.00	-0.34+	-0.01	0.00	-0.36*
	ε4				-0.02	0.04	-0.10	-0.03	0.04	-0.12	-0.02	0.04	-0.10
	CR2							0.03	0.04	0.11	-0.03	0.04	-0.11
	ε4 x CR2										0.07	0.03	0.46*
	R^2		0.12			0.13			0.15			0.31	
	F		4.62*			2.46			1.75			3.30*	
	$R^2\Delta$					0.01			0.01			0.16	
	F Δ					0.38			0.42			6.92*	
C. LH Pars Triangularis	Age	0.00	0.00	-0.13	0.00	0.00	-0.15	0.00	0.00	-0.16	0.00	0.00	-0.18
	ε4				0.04	0.05	0.14	0.03	0.05	0.11	0.03	0.04	0.13
	CR2							0.07	0.05	0.28	0.01	0.05	0.05
	ε4 x CR2										0.08	0.03	0.47*
	R^2		0.02			0.04			0.11			0.28	
	F		0.54			0.60			1.28			2.90*	
	$R^2\Delta$					0.02			0.07			0.17	
	F Δ					0.67			2.57			7.02*	

Notes: +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; MFG=Middle Frontal Gyrus

Table 16

CR2 Post Hoc Hierarchical Regression Analyses Predicting Parietal Label Thickness Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. LH Inferior Parietal	Age	-0.01	0.00	-0.43*	-0.01	0.00	-0.43*	-0.01	0.00	-0.44**	-0.01	0.00	-0.46**
	ε4				0.00	0.04	-0.01	-0.01	0.04	-0.04	-0.01	0.04	-0.02
	CR2							0.07	0.04	0.25	0.01	0.04	0.04
	ε4 x CR2										0.08	0.03	0.44*
	R^2		0.18			0.18			0.25			0.40	
	F		7.38*			3.58*			3.36*			4.93**	
	R^2 Δ					0.00			0.06			0.15	
	F Δ					0.00			2.58			7.51*	
B. LH Insula	Age	0.00	0.00	-0.23	0.00	0.00	-0.24	0.00	0.00	-0.23	0.00	0.00	-0.24
	ε4				0.01	0.05	0.03	0.01	0.06	0.04	0.02	0.05	0.05
	CR2							-0.02	0.06	-0.07	-0.07	0.06	-0.23
	ε4 x CR2										0.07	0.04	0.33+
	R^2		0.05			0.06			0.06			0.14	
	F		1.87			0.92			0.65			1.26	
	R^2 Δ					0.00			0.00			0.09	
	F Δ					0.03			0.15			2.98+	
C. RH Insula	Age	-0.01	0.00	-0.33+	-0.01	0.00	-0.33+	-0.01	0.00	-0.33+	-0.01	0.00	-0.34+
	ε4				0.00	0.06	-0.01	-0.01	0.06	-0.02	0.00	0.06	-0.01
	CR2							0.03	0.06	0.09	-0.02	0.07	-0.06
	ε4 x CR2										0.07	0.04	0.31
	R^2		0.11			0.11			0.11			0.19	
	F		3.95+			1.92			1.33			1.71	
	R^2 Δ					0.00			0.01			0.07	
	F Δ					0.01			0.25			2.62	

Notes: +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; RH=Right Hemisphere

Table 17

CR2 Post Hoc Regression Predicting Left Hippocampus Label Volume

		Model 1			**Model 2**			**Model 3**			**Model 4**		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
LH Hippocampus	Age	-17.32	9.16	-0.31+	-16.64	9.39	-0.30+	-16.46	9.54	-0.30+	-17.03	9.30	-0.31+
	ε4				-76.53	168.80	-0.08	-68.65	172.66	-0.07	-56.13	168.39	-0.06
	CR2							-59.30	170.36	-0.06	-207.54	189.22	-0.21
	ε4 x CR2										209.13	128.20	0.31
	R^2		0.10			0.10			0.11			0.18	
	F		3.57+			1.85			1.24			1.64	
	R^2 Δ					0.01			0.00			0.07	
	F Δ					0.21			0.12			0.27	

Notes: +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere

Table 18

CR3 FPN Label Thickness ANCOVA Results

	1. Left Hemisphere				2. Right Hemisphere			
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. Rostral MFG	ε4	0.12	0.00	0.73	ε4	0.38	0.01	0.54
	CR3	3.61+	0.11	0.07	CR3	1.44	0.05	0.24
	ε4 x CR3	5.55*	0.16	0.03	ε4 x CR3	3.87+	0.11	0.06
	Age (Covariate)	0.33	0.01	0.57	Age (Covariate)	0.10	0.00	0.75
B. Caudal ACC	ε4	0.17	0.01	0.69	ε4	0.80	0.03	0.38
	CR3	0.00	0.00	0.96	CR3	0.13	0.00	0.72
	ε4 x CR3	0.58	0.02	0.45	ε4 x CR3	1.95	0.06	0.17
	Age (Covariate)	1.57	0.05	0.22	Age (Covariate)	0.00	0.00	0.96
C. Rostral ACC	ε4	0.03	0.00	0.87	ε4	0.00	0.00	0.97
	CR3	0.00	0.00	0.96	CR3	0.28	0.01	0.60
	ε4 x CR3	0.06	0.00	0.81	ε4 x CR3	2.18	0.07	0.15
	Age (Covariate)	1.00	0.03	0.32	Age (Covariate)	0.57	0.02	0.46
D. Pars Opercularis	ε4	0.99	0.03	0.33	ε4	0.09	0.00	0.77
	CR3	3.11+	0.09	0.09	CR3	0.72	0.02	0.40
	ε4 x CR3	3.44+	0.10	0.07	ε4 x CR3	0.01	0.00	0.93
	Age (Covariate)	1.62	0.05	0.21	Age (Covariate)	4.23*	0.12	0.05
E. Pars Orbitalis	ε4	0.55	0.02	0.47	ε4	0.58	0.02	0.45
	CR3	2.59	0.08	0.12	CR3	0.04	0.00	0.85
	ε4 x CR3	0.82	0.03	0.37	ε4 x CR3	0.03	0.00	0.87
	Age (Covariate)	0.04	0.00	0.84	Age (Covariate)	9.55**	0.24	0.00
F. Pars Triangularis	ε4	0.14	0.00	0.72	ε4	2.00	0.06	0.17
	CR3	11.11**	0.27	0.00	CR3	5.05*	0.14	0.03
	ε4 x CR3	1.93	0.06	0.18	ε4 x CR3	1.01	0.03	0.32
	Age (Covariate)	0.07	0.00	0.79	Age (Covariate)	3.46+	0.10	0.07
G. Inferior Parietal	ε4	0.15	0.01	0.70	ε4	0.00	0.00	0.98
	CR3	3.55+	0.11	0.07	CR3	1.96	0.06	0.17
	ε4 x CR3	1.75	0.06	0.20	ε4 x CR3	1.18	0.04	0.29
	Age (Covariate)	3.47+	0.10	0.07	Age (Covariate)	4.70*	0.14	0.04
H. Superior Parietal	ε4	0.71	0.02	0.41	ε4	0.36	0.01	0.55
	CR3	0.96	0.03	0.34	CR3	1.66	0.05	0.21
	ε4 x CR3	1.50	0.05	0.23	ε4 x CR3	0.74	0.02	0.40
	Age (Covariate)	4.18+	0.12	0.05	Age (Covariate)	2.61	0.08	0.12
I. Insula	ε4	0.00	0.00	0.97	ε4	0.14	0.01	0.71
	CR3	0.44	0.01	0.51	CR3	1.66	0.05	0.21
	ε4 x CR3	6.37*	0.18	0.02	ε4 x CR3	4.84*	0.14	0.04
	Age (Covariate)	0.90	0.03	0.35	Age (Covariate)	1.74	0.06	0.20

Notes: +p<0.10, *p<0.05, **p<0.01; MFG=Middle Frontal Gyrus; ACC=Anterior CingulateCortex

Table 19

CR3 MTL/HC Label Thickness ANCOVA Results

	1. Left Hemisphere				2. Right Hemisphere			
	Main Effects	***F***	**$\eta_p 2$**	***p***	**Main Effects**	***F***	**$\eta_p 2$**	***p***
A. HC	ε4	0.14	0.01	0.71	ε4	1.97	0.06	0.17
	CR3	0.12	0.00	0.73	CR3	0.03	0.00	0.87
	ε4 x CR3	0.01	0.00	0.93	ε4 x CR3	0.07	0.00	0.79
	Age (Covariate)	3.01+	0.09	0.09	Age (Covariate)	1.29	0.04	0.27
B. PHG	ε4	0.39	0.01	0.54	ε4	0.05	0.00	0.82
	CR3	0.54	0.02	0.47	CR3	0.01	0.00	0.91
	ε4 x CR3	0.55	0.02	0.46	ε4 x CR3	4.25*	0.12	0.05
	Age (Covariate)	0.41	0.01	0.53	Age (Covariate)	6.02*	0.17	0.02
C. Entorhinal	ε4	0.83	0.03	0.37	ε4	0.29	0.01	0.55
	CR3	0.38	0.01	0.54	CR3	0.22	0.01	0.64
	ε4 x CR3	0.06	0.00	0.81	ε4 x CR3	0.12	0.00	0.73
	Age (Covariate)	1.40	0.05	0.25	Age (Covariate)	2.87	0.09	0.10

Notes: +p<0.10, *p<0.05, **p<0.01; HC=Hippocampus; PHG=Parahippocampal Gyrus

Table 20

CR3 Post Hoc Regressions Predicting LH FPN Label Thickness

		Model 1			Model 2			Model 3			Model 3		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. LH Rostral MFG	Age	0.00	0.00	-0.21	0.00	0.00	-0.23	0.00	0.00	-0.15	0.00	0.00	-0.08
	ε4				0.03	0.05	0.12	0.02	0.05	0.08	0.03	0.05	0.12
	CR3							0.07	0.05	0.27	0.02	0.05	0.07
	ε4 x CR3										0.07	0.04	0.40*
	R^2		0.05			0.06			0.12			0.24	
	F		1.59			1.02			1.46			2.31+	
	$R^2\,\Delta$					0.01			0.06			0.11	
	F Δ					0.47			2.28			4.37*	
B. LH Pars Triangularis	Age	0.00	0.00	-0.13	0.00	0.00	-0.15	0.00	0.00	0.02	0.00	0.00	0.05
	ε4				0.04	0.05	0.14	0.02	0.04	0.07	0.02	0.04	0.09
	CR3							0.13	0.04	0.51**	0.11	0.05	0.41*
	ε4 x CR3										0.04	0.03	0.20
	R^2		0.02			0.04			0.27			0.30	
	F		0.54			0.60			3.79*			3.16*	
	$R^2\,\Delta$					0.02			0.23			0.03	
	F Δ					0.67			9.84**			1.18	
C. LH Insula	Age	0.00	0.00	-0.23	0.00	0.00	-0.24	0.00	0.00	-0.22	0.00	0.00	-0.17
	ε4				0.01	0.05	0.03	0.01	0.06	0.02	0.02	0.06	0.05
	CR3							0.02	0.06	0.06	-0.02	0.07	-0.08
	ε4 x CR3										0.06	0.04	0.28
	R^2		0.05			0.06			0.06			0.11	
	F		1.87			0.92			0.63			0.94	
	$R^2\,\Delta$					0.00			0.00			0.05	
	F Δ					0.03			0.10			1.83	

Notes: +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; RH=Right Hemisphere; MFG=Middle Frontal Gyrus

Table 21

CR3 Post Hoc Regression Predicting Right Hemisphere FPN/PHG Label Thickness

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. RH Pars Triangularis	Age	-0.01	0.00	-0.50*	-0.01	0.00	-0.42*	-0.01	0.00	-0.32+	-0.01	0.00	-0.23+
	ε4				-0.06	0.06	-0.16	-0.08	0.06	-0.20	-0.07	0.06	-0.20
	CR3							0.13	0.06	0.34*	0.11	0.07	0.29
	ε4 x CR3										0.03	0.05	0.10
	R^2		0.20			0.23			0.33			0.33	
	F		8.339**			4.66*			4.98**			3.73*	
	R^2 Δ					0.02			0.10			0.01	
	F Δ					0.99			4.570*			0.32	
B. RH Insula	Age	-0.01	0.00	-0.33+	-0.01	0.00	-0.33+	-0.01	0.00	-0.27	0.00	0.00	-0.21
	ε4				0.00	0.06	-0.01	-0.01	0.06	-0.04	0.00	0.06	0.00
	CR3							0.06	0.06	0.17	0.00	0.07	-0.01
	ε4 x CR3										0.09	0.04	0.37+
	R^2		0.11			0.11			0.13			0.23	
	F		3.95+			1.92			1.58			2.19+	
	R^2 Δ					0.00			0.03			0.09	
	F Δ					0.00			0.92			3.62+	
C. RH Inferior Parietal	Age	-0.01	0.00	-0.45**	-0.01	0.00	-0.46**	-0.01	0.00	-0.39*	-0.01	0.00	-0.33+
	ε4				0.01	0.05	0.05	0.01	0.05	0.02	0.02	0.05	0.05
	CR3							0.06	0.05	0.21	0.01	0.05	0.02
	ε4 x CR3										0.08	0.04	0.39*
	R^2		0.20			0.20			0.24			0.35	
	F		8.28**			4.07*			3.30*			3.99*	
	R^2 Δ					0.00			0.04			0.11	
	F Δ					0.08			1.61			4.84*	
D. RH Superior Parietal	Age	-0.01	0.00	-0.35*	-0.01	0.00	-0.37*	0.00	0.00	-0.30+	0.00	0.00	-0.24
	ε4				0.04	0.04	0.14	0.03	0.04	0.11	0.04	0.04	0.15
	CR3							0.06	0.05	0.21	0.01	0.05	0.02
	ε4 x CR3										0.07	0.03	0.39*
	R^2		0.12			0.14			0.18			0.28	
	F		4.55*			2.61+			2.24			2.95*	
	R^2 Δ					0.02			0.04			0.10	
	F Δ					0.71			1.43			4.35*	
E. RH PHG	Age	-0.01	0.01	-0.43*	-0.01	0.01	-0.43*	-0.01	0.01	-0.45*	-0.01	0.01	-0.43*
	ε4				-0.01	0.09	-0.02	-0.01	0.09	-0.02	0.00	0.09	0
	CR3							-0.03	0.09	-0.06	-0.07	0.11	-0.13
	ε4 x CR3										0.05	0.07	0.14
	R^2		0.19			0.19			0.19			0.2	
	F		7.54*			3.67*			2.42+			1.91	
	R^2 Δ					0			0			0.01	
	F Δ					0.02			0.13			0.49	

Notes: +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; RH=Right Hemisphere; PHG=Parahippocampal Gyrus

Table 22

CR1 Vertex Analysis Post Hoc Hierarchical Regressions for LH Lateral Parietal

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 1-LH Insula	Age	-0.01	0.00	-0.37*	-0.01	0.00	-0.38*	-0.01	0.00	-0.37*	-0.01	0.00	-0.33*
	ε4				0.03	0.07	0.07	0.03	0.07	0.07	0.02	0.06	0.06
	CR1							-0.01	0.03	-0.04	-0.10	0.04	-0.50*
	ε4 x CR1										0.20	0.06	0.68**
	R^2		0.13			0.14			0.14			0.40	
	F		5.06*			2.54+			1.67			4.92**	
	R^2 Δ					0.00			0.00			0.26	
	F Δ					0.16			0.06			12.77**	
B. 2–LH Superior Parietal	Age	-0.01	0.00	-0.34*	-0.01	0.00	-0.36*	-0.01	0.01	-0.37*	-0.01	0.00	-0.33*
	ε4				0.07	0.08	0.15	0.07	0.08	0.15	0.07	0.08	0.14
	CR1							0.03	0.04	0.14	-0.05	0.05	-0.19
	ε4 x CR1										0.18	0.08	0.49*
	R^2		0.11			0.14			0.15			0.29	
	F		4.23*			2.52+			1.89			2.30*	
	R^2 Δ					0.02			0.02			0.13	
	F Δ					0.83			0.67			5.51*	
C. 3- LHInferior Parietal	Age	-0.01	0.00	-0.31+	-0.01	0.00	-0.31+	-0.01	0.00	-0.32+	-0.01	0.00	-0.27+
	ε4				0.00	0.08	-0.01	-0.01	0.08	-0.01	-0.01	0.07	-0.02
	CR1							0.05	0.04	0.21	-0.06	0.05	-0.24
	ε4 x CR1										0.24	0.07	0.68**
	R^2		0.10			0.10			0.14			0.40	
	F		3.60+			1.75			1.72			4.93**	
	R^2 Δ					0.00			0.04			0.25	
	F Δ					0.00			1.60			12.62**	
D. 4–LH Inferior Parietal	Age	-0.01	0.01	-0.28	-0.01	0.01	-0.26	-0.01	0.01	-0.27	-0.01	0.01	-0.22
	ε4				-0.06	0.10	-0.10	-0.06	0.11	-0.10	-0.07	0.09	-0.11
	CR1							0.03	0.05	0.10	-0.12	0.06	-0.39*
	ε4 x CR1										0.34	0.09	0.74**
	R^2		0.08			0.09			0.10			0.39	
	F		2.75			1.50			1.09			4.85**	
	R^2 Δ					0.01			0.01			0.30	
	F Δ					0.31			0.34			14.66**	
E. 5–LH Superior Parietal	Age	0.00	0.00	-0.22	0.00	0.00	-0.22	0.00	0.00	-0.23	0.00	0.00	-0.18
	ε4				0.01	0.06	0.02	0.00	0.06	0.01	0.00	0.05	0.00
	CR1							0.04	0.03	0.22	-0.04	0.03	-0.22
	ε4 x CR1										0.17	0.05	0.65**
	R^2		0.05			0.05			0.10			0.33	
	F		1.66			0.81			1.10			3.71*	
	R^2 Δ					0.00			0.05			0.24	
	F Δ					0.01			1.66			10.52**	
F. 6–LH Caudal ACC	Age	0.00	0.01	0.07	0.01	0.01	0.12	0.00	0.01	0.11	0.01	0.01	0.14
	ε4				-0.19	0.12	-0.28	-0.20	0.12	-0.28	-0.20	0.11	-0.29+
	CR1							0.09	0.06	0.26	-0.04	0.07	-0.11
	ε4 x CR1										0.29	0.11	0.56**
	R^2		0.01			0.08			0.15			0.32	
	F		0.17			1.37			1.77			3.48*	
	R^2 Δ					0.07			0.07			0.17	
	F Δ					2.56			2.45			7.48**	

Notes: Numbers assigned to regions in the rows correspond to Figures 4-7. +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; ACC=Anterior Cingulate Cortex

Table 23

CR1 Vertex Analysis Post Hoc Hierarchical Regressions for Right Hemisphere Regions with Significant Interaction Effects.

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 8–RH Insula	Age	0.00	0.01	0.01	0.00	0.01	0.02	0.00	0.01	0.02	0.00	0.01	0.06
	ε4				-0.10	0.18	-0.10	-0.11	0.18	-0.11	-0.12	0.17	-0.11
	CR1							0.06	0.09	0.12	-0.13	0.11	-0.26
	ε4 x CR1										0.43	0.17	0.57*
	R^2		0.00			0.01			0.02			0.20	
	F		0.00			0.17			0.26			1.92	
	$R^2\,\Delta$					0.01			0.01			0.18	
	F Δ					0.33			0.44			6.75*	
B. 9–RH Inferior Parietal	Age	-0.01	0.00	-0.22	-0.01	0.00	-0.21	-0.01	0.00	-0.21	0.00	0.00	-0.16
	ε4				-0.03	0.08	-0.06	-0.03	0.08	-0.06	-0.03	0.07	-0.08
	CR1							0.03	0.04	0.12	-0.09	0.05	-0.38+
	ε4 x CR1										0.26	0.07	0.74**
	R^2		0.05			0.05			0.07			0.37	
	F		1.66			0.87			0.72			4.37**	
	$R^2\,\Delta$					0.00			0.01			0.30	
	F Δ					0.12			0.44			14.41**	
C. 10–RH Superior Parietal	Age	-0.01	0.00	-0.20	-0.01	0.00	-0.21	-0.01	0.00	-0.22	0.00	0.00	-0.18
	ε4				0.04	0.08	0.09	0.04	0.08	0.08	0.03	0.07	0.07
	CR1							0.05	0.04	0.24	-0.04	0.05	-0.19
	ε4 x CR1										0.22	0.07	0.64**
	R^2		0.04			0.05			0.10			0.33	
	F		1.32			0.77			1.20			3.71*	
	$R^2\,\Delta$					0.01			0.06			0.23	
	F Δ					0.25			2.02			10.16**	
D. 13-RH Caudal ACC	Age	0.00	0.01	0.00	0.00	0.01	0.03	0.00	0.01	0.01	0.00	0.01	0.05
	ε4				-0.17	0.19	-0.16	-0.18	0.18	-0.17	-0.19	0.16	-0.18
	CR1							0.20	0.09	0.37*	-0.01	0.11	-0.02
	ε4 x CR1										0.48	0.16	0.58**
	R^2		0.00			0.02			0.16			0.35	
	F		0.00			0.40			1.96			3.96*	
	$R^2\,\Delta$					0.02			0.14			0.19	
	F Δ					0.80			4.99*			8.51**	

Notes: Numbers assigned to regions in the rows correspond to Figures 4-7. +p<0.10, *p<0.05, **p<0.01; RH=Right Hemisphere ACC=Anterior Cingulate Cortex; PHG=Parahippocamal Gyrus

Table 24

CR1 Vertex Analysis Post hoc Hierarchical Regressions for Right Hemisphere Regions with Non-Significant Interaction Effects.

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 7-RH Rostral MFG	Age	-0.01	0.01	-0.31+	-0.01	0.01	-0.33+	-0.01	0.01	-0.33+	-0.01	0.01	-0.30+
	ε4				0.08	0.11	0.12	0.08	0.11	0.12	0.07	0.11	0.11
	CR1							0.00	0.06	0.00	-0.10	0.07	-0.29
	ε4 x CR1										0.21	0.11	0.43+
	R^2		0.09			0.11			0.11			0.21	
	F		3.41+			1.93			1.25			2.01	
	$R^2\Delta$					0.01			0.00			0.10	
	F Δ					0.50			0.00			3.93+	
B. 11-RH Superior Parietal	Age	0.00	0.01	0.06	0.00	0.01	0.06	0.00	0.01	0.06	0.00	0.01	0.08
	ε4				-0.02	0.12	-0.02	-0.02	0.12	-0.03	-0.02	0.12	-0.03
	CR1							0.04	0.06	0.13	-0.04	0.08	-0.11
	ε4 x CR1										0.18	0.12	0.35
	R^2		0.00			0.00			0.02			0.09	
	F		0.11			0.06			0.22			0.73	
	$R^2\Delta$					0.00			0.02			0.07	
	F Δ					0.02			0.52			2.24	
C. 12-RH Superior Parietal	Age	0.00	0.01	-0.01	0.00	0.01	-0.04	0.00	0.01	-0.04	0.00	0.01	-0.01
	ε4				0.10	0.08	0.20	0.10	0.08	0.20	0.09	0.08	0.20
	CR1							-0.03	0.04	-0.12	-0.08	0.05	-0.35
	ε4 x CR1										0.12	0.08	0.35
	R^2		0.00			0.04			0.05			0.12	
	F		0.00			0.66			0.58			1.01	
	$R^2\Delta$					0.04			0.01			0.07	
	F Δ					1.31			0.44			2.25	
D. 14-RH PHG	Age	0.00	0.01	-0.01	0.00	0.01	-0.06	0.00	0.01	-0.07	0.00	0.01	-0.04
	ε4				0.19	0.10	0.31+	0.19	0.11	0.31+	0.19	0.10	0.31+
	CR1							0.01	0.05	0.04	-0.07	0.07	-0.23
	ε4 x CR1										0.18	0.10	0.40+
	R^2		0.00			0.10			0.10			0.19	
	F		0.01			1.71			1.12			1.71	
	$R^2\Delta$					0.10			0.00			0.09	
	F Δ					3.41+			0.04			3.23+	

Notes: Numbers assigned to regions in the rows correspond to Figures 4-7. +p<0.10, *p<0.05, **p<0.01; RH=Right Hemisphere; MFG=Middle Frontal Gyrus

Table 25

CR2 Vertex Analysis Post hoc Regressions for Left Hemisphere Frontal Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 1-LH Rostral MFG	Age	0.00	0.00	-0.07	0.00	0.00	-0.10	0.00	0.00	-0.12	0.00	0.00	-0.11
	ε4				0.06	0.06	0.19	0.06	0.06	0.18	0.06	0.05	0.18
	CR2							0.04	0.03	0.23	-0.05	0.04	-0.30
	ε4 x CR2										0.16	0.05	0.72**
	R^2		0.00			0.04			0.09			0.33	
	F		0.14			0.66			1.06			3.65*	
	$R^2\Delta$					0.04			0.05			0.23	
	F Δ					1.18			1.81			10.44**	
B. 4-LH Rostral MFG	Age	-0.01	0.01	-0.33*	-0.01	0.01	-0.36*	-0.01	0.01	-0.34*	-0.01	0.00	-0.34*
	ε4				0.09	0.09	0.16	0.09	0.09	0.16	0.09	0.08	0.16
	CR2							-0.06	0.05	-0.21	-0.20	0.06	-0.72**
	ε4 x CR2										0.27	0.08	0.70**
	R^2		0.11			0.14			0.18			0.40	
	F		4.15*			2.51+			2.25			5.02**	
	$R^2\Delta$					0.02			0.04			0.22	
	F Δ					0.87			1.64			11.12**	
C. 3-LH Pars Triangularis	Age	0.00	0.00	-0.17	0.00	0.00	-0.15	0.00	0.00	-0.18	0.00	0.00	-0.17
	ε4				-0.03	0.05	-0.11	-0.03	0.05	-0.11	-0.03	0.04	-0.11
	CR2							0.04	0.02	0.26	-0.02	0.03	-0.16
	ε4 x CR2										0.11	0.04	0.58*
	R^2		0.03			0.04			0.11			0.26	
	F		0.99			0.66			1.25			2.61+	
	$R^2\Delta$					0.01			0.07			0.15	
	F Δ					0.87			1.64			11.12**	
D. 11. LH Caudal ACC	Age	0.00	0.01	0.09	0.00	0.01	0.11	0.00	0.01	0.11	0.00	0.01	0.12
	ε4				-0.06	0.10	-0.12	-0.06	0.10	-0.11	-0.06	0.09	-0.12
	CR2							-0.01	0.05	-0.03	-0.15	0.07	-0.53*
	ε4 x CR2										0.26	0.09	0.68**
	R^2		0.01			0.02			0.02			0.23	
	F		0.28			0.35			0.23			2.28+	
	$R^2\Delta$					0.01			0.00			0.21	
	F Δ					0.42			0.03			8.27**	

Notes: Numbers assigned to regions in the rows correspond to Figures 9-12; +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; RH=Right Hemisphere; MFG=Middle Frontal Gyrus; ACC= Anterior Cingulate Cortex

Table 26

CR2 Vertex Analysis Post hoc Hierarchical Regressions for Left Parietal Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 5-LH Insula	Age	0.01	0.01	0.14	0.01	0.01	0.14	0.01	0.01	0.11	0.01	0.01	0.12
	ε4				0.02	0.13	0.02	0.01	0.13	0.01	0.01	0.12	0.01
	CR2							0.11	0.06	0.30+	-0.05	0.09	-0.13
	ε4 x CR2										0.29	0.12	0.58*
	R^2		0.02			0.02			0.11			0.26	
	F		0.69			0.34			1.28			2.70*	
	$R^2\Delta$					0.00			0.09			0.15	
	F Δ					0.01			3.11+			6.29*	
B. 6-LH Insula	Age	-0.01	0.00	-0.51**	-0.01	0.00	-0.53**	-0.01	0.00	-0.52**	-0.01	0.00	-0.52**
	ε4				0.04	0.05	0.13	0.04	0.05	0.13	0.04	0.04	0.13
	CR2							0.00	0.02	-0.02	-0.09	0.03	-0.61**
	ε4 x CR2										0.16	0.04	0.80**
	R^2		0.26			0.27			0.27			0.56	
	F		11.37**			5.97**			3.87*			9.65**	
	$R^2\Delta$					0.02			0.00			0.29	
	F Δ					0.68			0.02			19.93**	
C. 8LH Inferior Parietal	Age	-0.01	0.00	-0.35*	-0.01	0.00	-0.35*	-0.01	0.00	-0.39*	-0.01	0.00	-0.38**
	ε4				0.00	0.07	0.00	-0.01	0.07	-0.02	-0.01	0.05	-0.02
	CR2							0.09	0.03	0.41*	-0.04	0.04	-0.16
	ε4 x CR2										0.23	0.05	0.76**
	R^2		0.13			0.13			0.29			0.55	
	F		4.72*			2.29			4.17*			9.28**	
	$R^2\Delta$					0.00			0.16			0.27	
	F Δ					9.00			7.07*			17.81**	
D. 9-LH Inferior Parietal	Age	-0.01	0.01	-0.22	-0.01	0.01	-0.21	-0.01	0.01	-0.21	-0.01	0.01	-0.21
	ε4				-0.07	0.12	-0.10	-0.07	0.12	-0.10	-0.07	0.11	-0.10
	CR2							0.02	0.06	0.05	-0.15	0.08	-0.44+
	ε4 x CR2										0.31	0.11	0.66**
	R^2		0.05			0.06			0.06			0.26	
	F		1.75			1.03			0.69			2.64+	
	$R^2\Delta$					0.01			0.00			0.20	
	F Δ					0.34			0.08			8.02**	
E. 7-LH Superior Parietal	Age	0.00	0.00	-0.21	0.00	0.00	-0.21	-0.01	0.00	-0.24	-0.01	0.00	-0.24+
	ε4				0.00	0.07	0.01	0.00	0.06	-0.01	0.00	0.05	-0.01
	CR2							0.08	0.03	0.40*	-0.03	0.04	-0.14
	ε4 x CR2										0.19	0.05	0.73**
	R^2		0.04			0.04			0.20			0.44	
	F		1.49			0.72			2.55+			5.86**	
	$R^2\Delta$					0.00			0.16			0.24	
	F Δ					0.00			5.98*			12.87**	
F. 10-LH Superior Parietal	Age	0.00	0.00	-0.21	0.00	0.00	-0.22	0.00	0.00	-0.24	0.00	0.00	-0.24
	ε4				0.01	0.06	0.04	0.01	0.06	0.03	0.01	0.05	0.03
	CR2							0.04	0.03	0.24	-0.06	0.04	-0.35
	ε4 x CR2										0.18	0.05	0.79**
	R^2		0.05			0.05			0.10			0.39	
	F		1.57			0.79			1.17			4.73**	
	$R^2\Delta$					0.00			0.06			0.29	
	F Δ					0.04			1.89			13.95**	

Notes: Numbers assigned to regions in the rows correspond to Figures 9-12; +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere

Table 27

CR2 Vertex Analysis Post Hoc Regressions for RH Parietal Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 13-RH Insula	Age	-0.01	0.01	-0.26	-0.01	0.01	-0.24	-0.01	0.01	-0.24	-0.01	0.01	-0.24
	ε4				-0.08	0.12	-0.12	-0.08	0.12	-0.12	-0.08	0.11	-0.12
	CR2							0.01	0.06	0.02	-0.16	0.08	-0.47*
	ε4 x CR2										0.31	0.11	0.67**
	R^2		0.07			0.08			0.08			0.28	
	F		2.32			1.37			0.89			2.95*	
	$R^2\Delta$					0.01			0.00			0.20	
	F Δ					0.47			0.02			8.48**	
B. 14-RH Insula	Age	0.02	0.01	0.42*	0.02	0.01	0.41*	0.02	0.01	0.40*	0.02	0.01	0.40*
	ε4				0.06	0.12	0.08	0.06	0.12	0.08	0.06	0.11	0.08
	CR2							0.04	0.06	0.10	-0.12	0.08	-0.33
	ε4 x CR2										0.28	0.11	0.57*
	R^2		0.18			0.18			0.19			0.34	
	F		7.12*			3.61*			2.48+			3.93*	
	$R^2\Delta$					0.01			0.01			0.15	
	F Δ					0.27			0.35			6.87*	
C. 16-RH Insula	Age	-0.01	0.00	-0.26	-0.01	0.00	-0.27	-0.01	0.00	-0.29	-0.01	0.00	-0.28
	ε4				0.02	0.07	0.04	0.01	0.07	0.03	0.01	0.07	0.03
	CR2							0.04	0.04	0.17	-0.07	0.05	-0.35
	ε4 x CR2										0.20	0.06	0.70**
	R^2		0.07			0.07			0.10			0.33	
	F		2.48			1.22			1.16			3.63*	
	$R^2\Delta$					0.00			0.03			0.23	
	F Δ					0.04			1.03			10.02**	
D. 17-RH Inferior Parietal	Age	-0.01	0.00	-0.26	-0.01	0.00	-0.27	-0.01	0.00	-0.28	-0.01	0.00	-0.27
	ε4				0.02	0.07	0.04	0.01	0.07	0.04	0.01	0.05	0.03
	CR2							0.03	0.03	0.14	-0.09	0.04	-0.50*
	ε4 x CR2										0.22	0.05	0.87**
	R^2		0.07			0.07			0.09			0.43	
	F		2.42			1.20			1.01			5.72**	
	$R^2\Delta$					0.00			0.02			0.34	
	F Δ					0.05			0.65			18.18**	
E. 18-RH Superior Parietal	Age	-0.01	0.00	-0.26	-0.01	0.00	-0.26	-0.01	0.00	-0.30+	-0.01	0.00	-0.29**
	ε4				0.00	0.05	0.01	0.00	0.05	-0.01	0.00	0.04	-0.01
	CR2							0.07	0.03	0.42*	-0.03	0.03	-0.19
	ε4 x CR2										0.18	0.04	0.83**
	R^2		0.07			0.07			0.24			0.56	
	F		2.41			1.17			3.33*			9.54**	
	$R^2\Delta$					0.00			0.18			0.32	
	F Δ					0.00			7.19*			21.56**	
F. 19-RH Superior Parietal	Age	0.00	0.01	-0.05	0.00	0.01	-0.06	0.00	0.01	-0.07	0.00	0.01	-0.07
	ε4				0.04	0.09	0.07	0.04	0.09	0.07	0.04	0.08	0.07
	CR2							0.04	0.05	0.14	-0.09	0.06	-0.34
	ε4 x CR2										0.23	0.08	0.65*
	R^2		0.00			0.01			0.03			0.22	
	F		0.08			0.12			0.28			2.13	
	$R^2\Delta$					0.01			0.02			0.19	
	F Δ					0.17			0.61			7.48*	

Notes: Numbers assigned to regions in the rows correspond to Figures 9-12; +p<0.10, *p<0.05, **p<0.01; RH=Right Hemisphere

Table 28

CR2 Vertex Analysis Post Hoc Hierarchical Regressions for Right Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 15-RH Pars Opercularis	Age	0.00	0.00	-0.06	0.00	0.00	-0.02	0.00	0.00	-0.03	0.00	0.00	-0.03
	ε4				-0.10	0.06	-0.27	-0.10	0.06	-0.27	-0.10	0.06	-0.27
	CR2							0.02	0.03	0.12	-0.06	0.04	-0.31
	ε4 x CR2										0.15	0.06	0.58*
	R^2		0.00			0.07			0.09			0.24	
	F		0.14			1.26			0.98			2.35+	
	$R^2 \Delta$					0.07			0.01			0.15	
	F Δ					2.38			0.46			6.00*	
B. 20-RH PHG	Age	-0.02	0.01	-0.35*	-0.02	0.01	-0.36*	-0.03	0.01	-0.37*	-0.03	0.01	-0.37*
	ε4				0.08	0.21	0.06	0.07	0.21	0.06	0.07	0.19	0.06
	CR2							0.09	0.10	0.15	-0.18	0.14	-0.29
	ε4 x CR2										0.50	0.19	0.60*
	R^2		0.12			0.12			0.15		0.31		
	F		4.46*			32.25			1.75			3.31*	
	$R^2 \Delta$					0.00			0.02			0.16	
	F Δ					0.15			0.79			6.99*	
C. 21-RH PHG	Age	-0.01	0.01	-0.37*	-0.01	0.01	-0.38*	-0.01	0.01	-0.36*	-0.01	0.01	-0.36*
	ε4				0.03	0.09	0.05	0.03	0.09	0.06	0.03	0.08	0.06
	CR2							-0.04	0.04	-0.16	-0.15	0.06	-0.57*
	ε4 x CR2										0.20	0.08	0.55*
	R^2		0.14			0.14			0.17			0.31	
	F		5.22*			2.58+			2.05			3.29*	
	$R^2 \Delta$					0.00			0.03			.14*	
	F Δ					0.09			0.99			6.00*	

Notes: Numbers assigned to regions in the rows correspond to Figures 9-12; +p<0.10, *p<0.05, **p<0.01; RH= Right Hemisphere PHG=Parahippocampal Gyrus

Table 29

CR3 Vertex Analysis Post Hoc Hierarchical Regressions for Left Frontal and Insular Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 1-LH Rostral MFG	Age	0.00	0.00	-0.21	0.00	0.00	-0.23	0.00	0.00	-0.13	0.00	0.00	-0.09
	ε4				0.05	0.06	0.16	0.06	0.06	0.17	0.05	0.05	0.16
	CR3							0.05	0.03	0.30	-0.05	0.04	-0.31
	ε4 x CR3										0.18	0.05	0.81**
	R^2		0.04			0.07			0.15			0.42	
	F		1.49			1.16			1.78			5.37**	
	$R^2\Delta$					0.02			0.08			0.27	
	F Δ					0.84			2.88			13.91**	
B. 2-LH Pars Opercularis	Age	0.00	0.00	-0.11	0.00	0.00	-0.10	0.00	0.00	-0.04	0.00	0.00	0.00
	ε4				-0.01	0.05	-0.04	-0.01	0.05	-0.03	-0.01	0.04	-0.04
	CR3							0.02	0.03	0.17	-0.05	0.03	-0.40
	ε4 x CR3										0.13	0.04	0.77**
	R^2		0.01			0.01			0.04			0.28	
	F		0.39			0.21			0.41			2.89*	
	$R^2\Delta$					0.00			0.03			0.24	
	F Δ					0.05			0.81			9.99**	
C. 3-LH Insula	Age	0.00	0.01	-0.08	0.00	0.01	-0.10	0.00	0.01	0.03	0.00	0.01	0.06
	ε4				0.10	0.14	0.13	0.11	0.13	0.14	0.11	0.12	0.14
	CR3							0.15	0.07	0.37*	-0.02	0.10	-0.04
	ε4 x CR3										0.28	0.13	0.55*
	R^2		0.01			0.02			0.14			0.27	
	F		0.23			0.37			1.71			2.70*	
	$R^2\Delta$					0.02			0.12			0.12	
	F Δ					0.52			4.32*			5.00*	
D. 4-LH Insula	Age	-0.01	0.00	-0.47**	-0.01	0.00	-0.51**	-0.01	0.00	-0.52**	-0.01	0.00	-0.49**
	ε4				0.07	0.06	0.20	0.07	0.06	0.20	0.07	0.05	0.20
	CR3							-0.01	0.03	-0.04	-0.08	0.04	-0.45+
	ε4 x CR3										0.13	0.05	0.55*
	R^2		0.22			0.26			0.27			0.39	
	F		9.49**			5.74**			3.74*			4.78**	
	$R^2\Delta$					0.04			0.00			0.12	
	F Δ					1.77			0.07			6.07*	

Notes: Numbers assigned to regions in the rows correspond to Figures 14-17; +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere; MFG=Middle Frontal Gyrus

Table 30

CR3 Vertex Analysis Post Hoc Hierarchical Regressions for Left Parietal Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 7-LH Inferior Parietal	Age	-0.01	0.00	-0.28+	-0.01	0.00	-0.29	-0.01	0.00	-0.20	0.00	0.00	-0.16
	ε4				0.01	0.07	0.02	0.01	0.07	0.03	0.01	0.07	0.02
	CR3							0.06	0.04	0.26	-0.06	0.05	-0.26
	ε4 x CR3										0.20	0.07	0.69**
	R^2		0.08			0.08			0.14			0.33	
	F		2.90+			1.41			1.65			3.73*	
	$R^2\Delta$					0.00			0.06			0.20	
	F Δ					0.12			2.03			8.74**	
B. 8-LH Inferior Parietal	Age	0.00	0.01	-0.07	0.00	0.01	-0.07	0.00	0.01	0.08	0.00	0.01	0.10
	ε4				-0.01	0.12	-0.02	0.00	0.12	0.00	-0.01	0.11	-0.01
	CR3							0.14	0.06	0.40*	0.00	0.09	-0.01
	ε4 x CR3										0.25	0.11	0.55*
	R^2		0.01			0.01			0.15			0.27	
	F		0.16			0.08			1.75			2.77*	
	$R^2\Delta$					0.00			0.14			0.13	
	F Δ					0.01			5.05*			5.12*	
C. 6-LH Superior Parietal	Age	0.00	0.00	-0.19	0.00	0.00	-0.20	0.00	0.00	-0.04	0.00	0.00	-0.01
	ε4				0.02	0.07	0.05	0.03	0.07	0.07	0.03	0.06	0.06
	CR3							0.09	0.04	0.46*	0.00	0.05	-0.01
	ε4 x CR3										0.17	0.06	0.63**
	R^2		0.04			0.04			0.22			0.38	
	F		1.24			0.64			2.90*			4.59**	
	$R^2\Delta$					0.00			0.18			0.16	
	F Δ					0.08			7.16*			7.76**	
D. 9-LH Superior Parietal	Age	0.00	0.00	-0.04	0.00	0.00	-0.04	0.00	0.00	0.04	0.00	0.00	0.07
	ε4				0.00	0.06	0.01	0.01	0.06	0.02	0.01	0.06	0.01
	CR3							0.04	0.03	0.22	-0.05	0.04	-0.31
	ε4 x CR3										0.16	0.06	0.70**
	R^2		0.00			0.00			0.04			0.25	
	F		0.06			0.03			0.47			2.44+	
	$R^2\Delta$					0.00			0.04			0.20	
	F Δ					0.01			1.36			8.02**	

Notes: Numbers assigned to regions in the rows correspond to Figures 14-17; +p<0.10, *p<0.05, **p<0.01; LH=Left Hemisphere

Table 31

CR3 Vertex Analysis Post Hoc Hierarchical Regressions for Right Frontal and Insular Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 11-RH Rostral MFG	Age	0.00	0.00	-0.04	0.00	0.00	-0.04	0.00	0.00	0.04	0.00	0.00	0.07
	ε4				0.01	0.07	0.02	0.01	0.07	0.03	0.01	0.07	0.02
	CR3							0.05	0.04	0.22	-0.05	0.05	-0.25
	ε4 x CR3										0.17	0.07	0.62*
	R^2		0.00			0.00			0.04			0.20	
	F		0.05			0.03			0.47			1.90	
	$R^2\Delta$					0.00			0.04			0.16	
	F Δ					0.01			1.36			5.94*	
B. 12-RH Rostral MFG	Age	0.00	0.00	-0.16	0.00	0.00	-0.18	0.00	0.00	-0.18	0.00	0.00	-0.15
	ε4				0.06	0.07	0.14	0.06	0.08	0.14	0.06	0.07	0.13
	CR3							0.00	0.04	0.01	-0.10	0.06	-0.46+
	ε4 x CR3										0.18	0.07	0.62*
	R^2		0.03			0.04			0.04			0.20	
	F		0.86			0.74			0.48			1.92	
	$R^2\Delta$					0.02			0.00			0.16	
	F Δ					0.63			0.00			6.00*	
C. 14-RH Pars Opercularis	Age	-0.01	0.00	-0.24	-0.01	0.00	-0.26	-0.01	0.01	-0.20	0.00	0.00	-0.17
	ε4				0.04	0.08	0.10	0.05	0.08	0.10	0.04	0.07	0.10
	CR3							0.04	0.04	0.17	-0.06	0.06	-0.26
	ε4 x CR3										0.17	0.07	0.57*
	R^2		0.06			0.07			0.09			0.22	
	F		2.01			1.14			1.02			2.13	
	$R^2\Delta$					0.01			0.02			0.13	
	F Δ					0.30			0.80			5.08*	
D. 15-RH Insula	Age	0.00	0.00	-0.06	0.00	0.00	-0.06	0.00	0.01	0.03	0.00	0.00	0.07
	ε4				-0.02	0.08	-0.05	-0.02	0.08	-0.04	-0.02	0.06	-0.05
	CR3							0.05	0.04	0.23	-0.09	0.05	-0.41
	ε4 x CR3										0.24	0.07	0.85**
	R^2		0.00			0.01			0.05			0.35	
	F		0.14			0.11			0.59			4.09**	
	$R^2\Delta$					0.00			0.05			0.30	
	F Δ					0.08			1.55			13.84**	

Notes: Numbers assigned to regions in the rows correspond to Figures 14-17; +p<0.10, *p<0.05, **p<0.01; RH=Right Hemisphere; MFG=middle frontal gyrus

Table 32

CR3 Vertex Analysis Post Hoc Hierarchical Regressions for Right Parietal Regions

		Model 1			Model 2			Model 3			Model 4		
	Variable	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***	***B***	***SE B***	***β***
A. 17-Inferior Parietal	Age	-0.01	0.01	-0.20	-0.01	0.01	-0.20	0.00	0.01	-0.15	0.00	0.01	-0.12
	ε4				-0.01	0.10	-0.03	-0.01	0.10	-0.02	-0.01	0.09	-0.03
	CR3							0.04	0.05	0.16	-0.08	0.07	-0.30
	ε4 x CR3										0.22	0.09	0.61*
	R^2		0.04			0.04			0.06			0.22	
	F		1.44			0.71			0.70			2.05	
	$R^2\Delta$					0.00			0.02			0.15	
	F Δ					0.02			0.71			5.77*	
B. 18-Inferior Parietal	Age	-0.01	0.01	-0.16	0.00	0.01	-0.13	0.00	0.01	0.01	0.00	0.01	0.03
	ε4				-0.13	0.11	-0.21	-0.12	0.10	-0.20	-0.12	0.10	-0.20
	CR3							0.12	0.05	0.39*	0.03	0.08	0.08
	ε4 x CR3										0.17	0.10	0.41
	R^2		0.03			0.07			0.20			0.27	
	F		0.86			1.18			2.56+			2.72*	
	$R^2\Delta$					0.04			0.13			0.07	
	F Δ					1.50			5.03*			2.76	
C. 16. Superior Parietal	Age	-0.01	0.00	-0.21	-0.01	0.00	-0.23	0.00	0.01	-0.17	0.00	0.00	-0.14
	ε4				0.07	0.08	0.15	0.07	0.08	0.16	0.07	0.07	0.15
	CR3							0.04	0.04	0.16	-0.08	0.05	-0.38
	ε4 x CR3										0.21	0.07	0.72**
	R^2		0.04			0.07			0.09			0.30	
	F		1.48			1.13			1.01			3.25*	
	$R^2\Delta$					0.02			0.02			0.21	
	F Δ					0.39			0.80			9.17**	
D. 19-Superior Parietal	Age	0.00	0.00	-0.22	0.00	0.00	-0.22	-0.01	0.00	-0.25	0.00	0.00	-0.22
	ε4				0.01	0.06	0.01	0.00	0.06	0.01	0.00	0.05	0.00
	CR3							-0.01	0.03	-0.08	-0.09	0.04	-0.55*
	ε4 x CR3										0.14	0.05	0.63*
	R^2		0.05			0.05			0.06			0.22	
	F		1.70			0.83			0.60			2.10	
	$R^2\Delta$					0.00			0.01			0.16	
	F Δ					0.01			0.19			6.29*	
E. 20-Superior Parietal	Age	-0.01	0.00	-0.39*	-0.01	0.00	-0.40*	-0.01	0.00	-0.29+	-0.01	0.00	-0.27
	ε4				0.02	0.07	0.04	0.02	0.07	0.06	0.02	0.06	0.05
	CR3							0.07	0.04	0.30+	-0.03	0.05	-0.15
	ε4 x CR3										0.17	0.06	0.59*
	R^2		0.15			0.16			0.23			0.38	
	F		5.99*			2.95+			3.13*			4.53**	
	$R^2\Delta$					0.00			0.08			0.14	
	F Δ					0.07			3.10+			6.94*	
F. 21-Superior Parietal	Age	0.00	0.00	-0.19	0.00	0.00	-0.19	0.00	0.00	-0.03	0.00	0.00	0.00
	ε4				0.02	0.07	0.05	0.03	0.06	0.07	0.03	0.06	0.06
	CR3							0.09	0.03	0.47**	0.01	0.05	0.03
	ε4 x CR3										0.15	0.06	0.59*
	R^2		0.04			0.04			0.23			0.37	
	F		1.18			0.61			3.06*			4.39**	
	$R^2\Delta$					0.00			0.19			0.14	
	F Δ					0.08			7.70**			6.67*	

Notes: +p<0.10, *p<0.05, **p<0.01

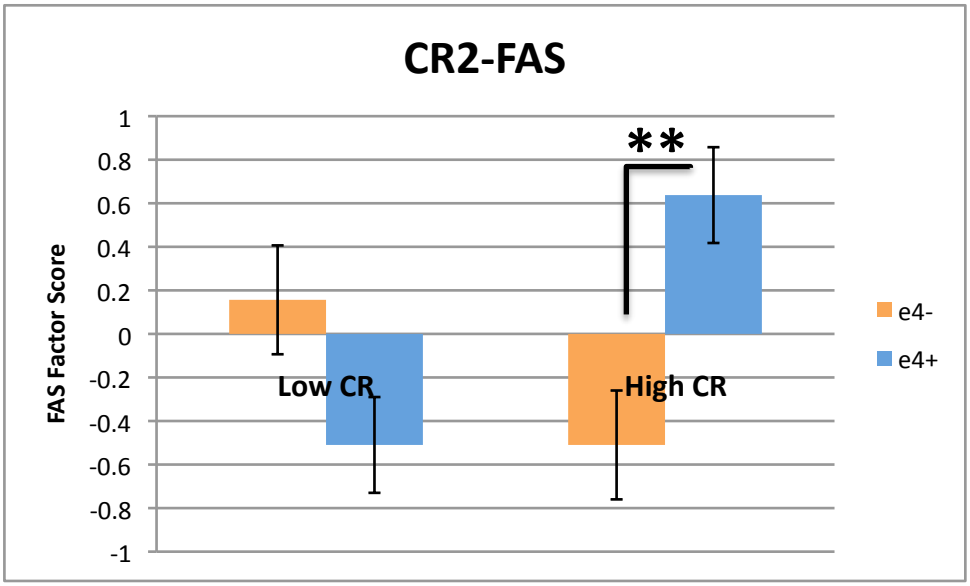


Figure 1: CR2 and FAS factor interaction graph shows the additive benefit mechanism.

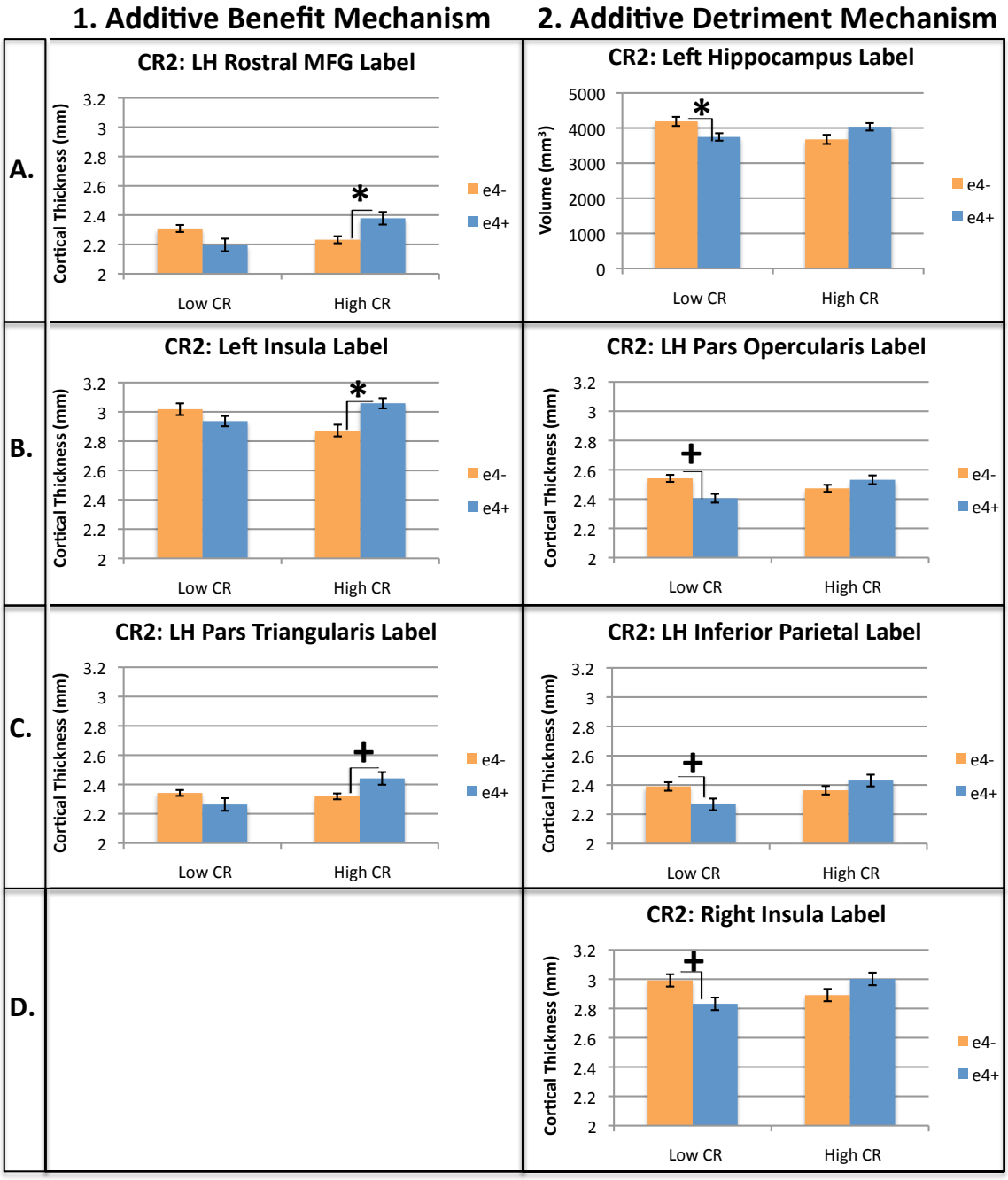


Figure 2: CR2 and ε4 interaction graphs from label analyses. The left column demonstrates the additive beneficial effect and the right column shows the additive detriment effect

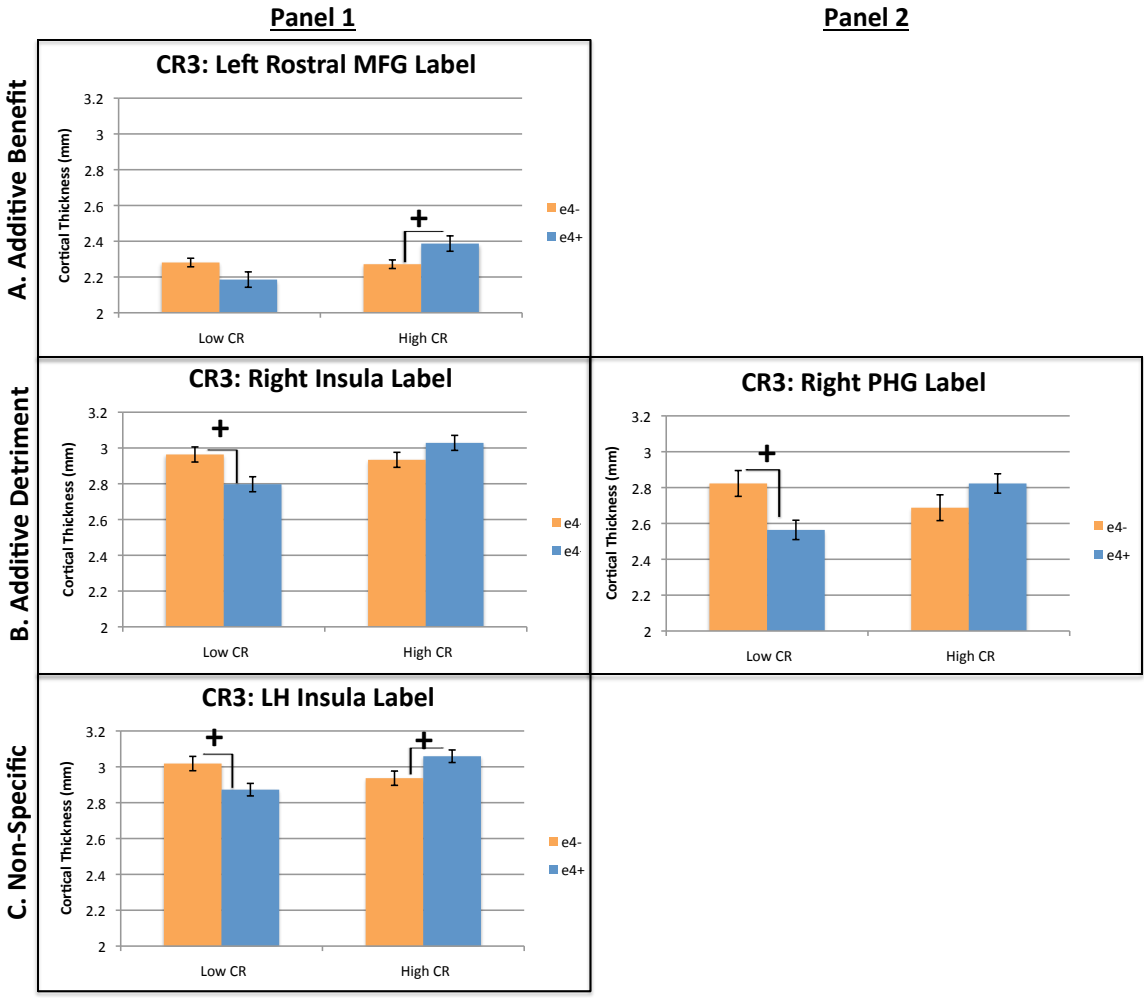


Figure 3: CR3 and ε4 interaction graphs from label analyses. The top panel shows the additive benefit mechanism, the middle panel shows the additive detriment mechanism and the lower panel shows that the left insula demonstrated both mechanisms.

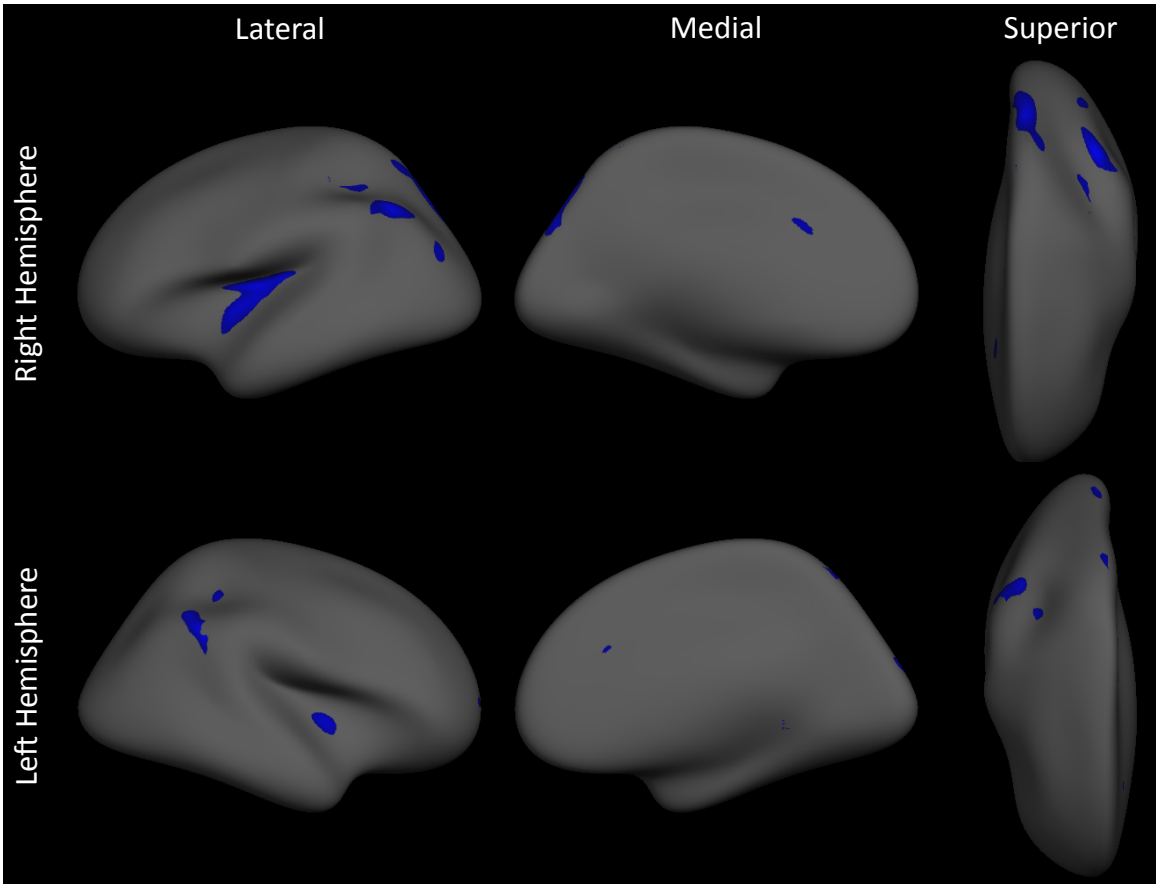


Figure 4. Results of bilateral CR1 vertex analysis. Blue regions show interactions between CR1 and ε4 (p<.0.05). Interactions were observed in bilateral insula, inferior and superior parietal regions, and anterior cingulate cortex

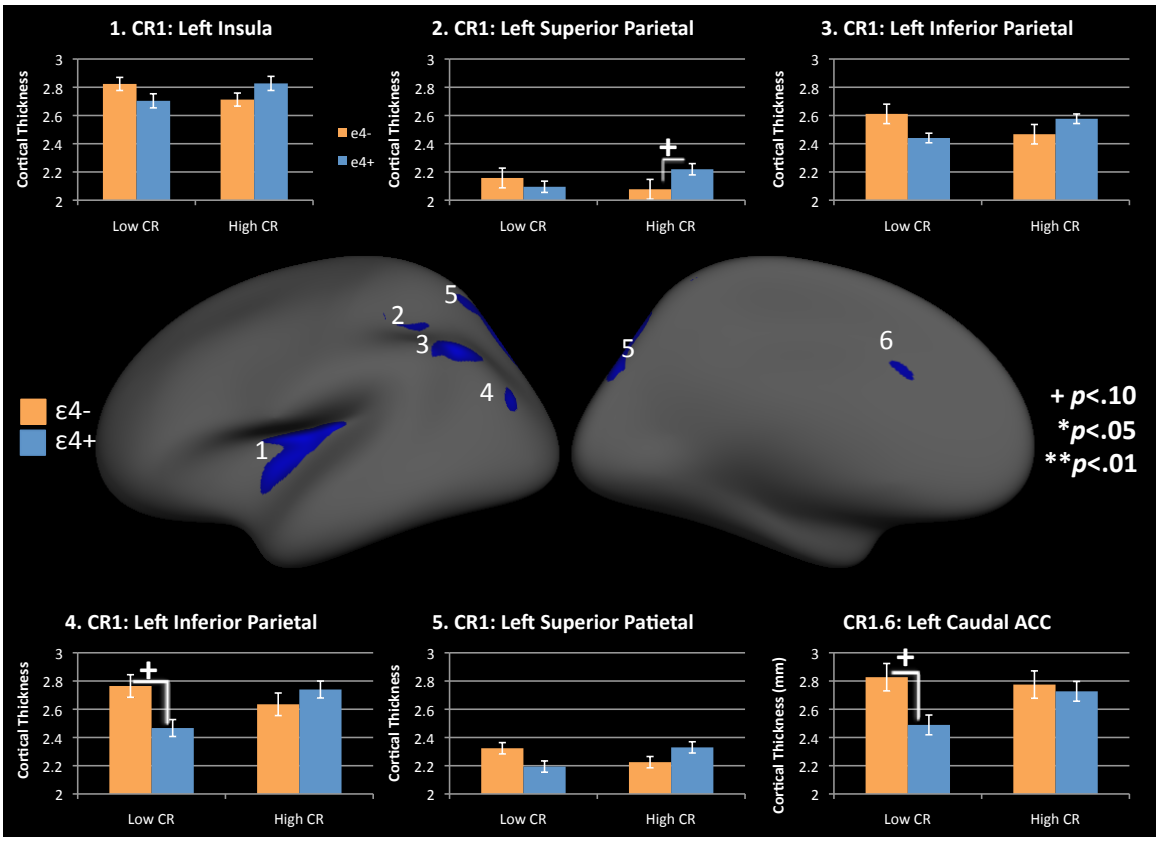


Figure 5: CR1 and ε4 interactions graphs are placed with their corresponding regions of significance in the left hemisphere (p<0.05). A statistical trend for the additive benefit mechanism was observed in the superior parietal. Statistical trends for the additive detriment mechanism were observed in regions of the inferior parietal and caudal anterior cingulate. Within groups differences were not observed in regions of the insula, inferior parietal, and superior parietal.

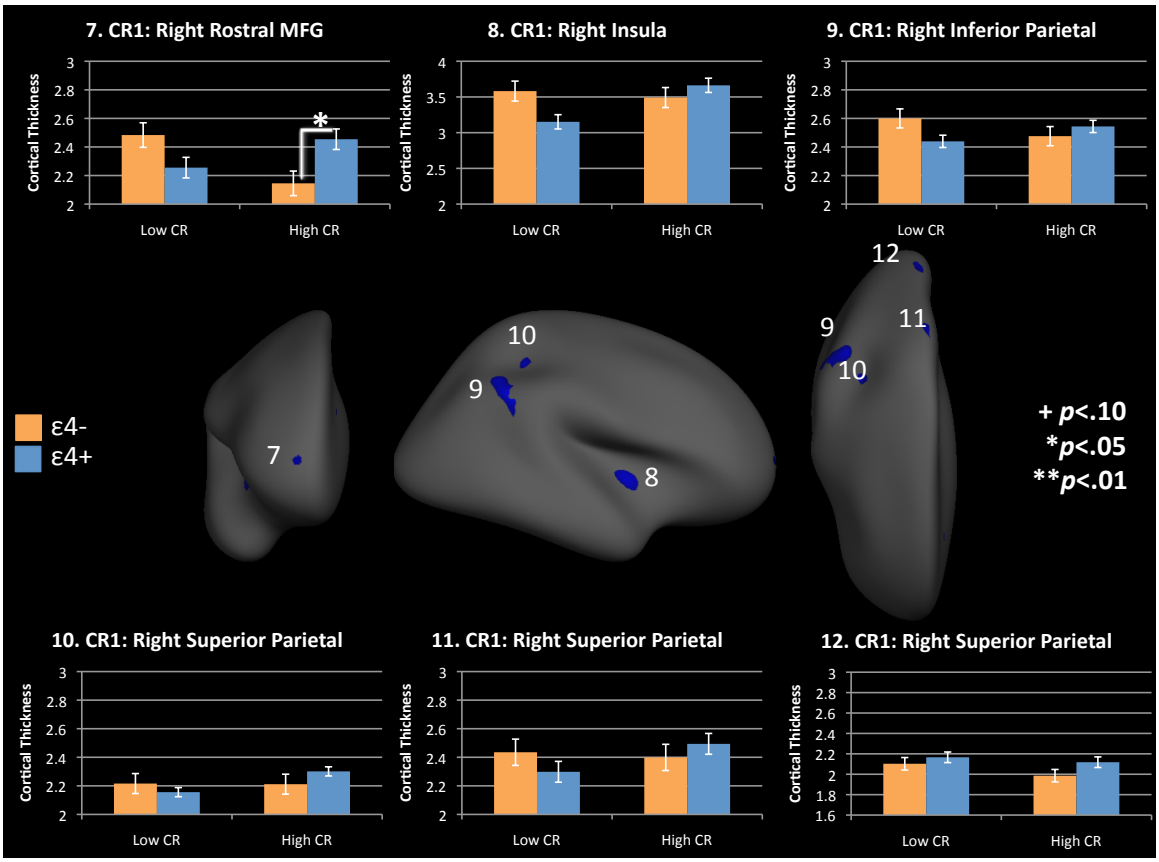


Figure 6: CR1 and e4 interactions graphs are placed with their corresponding regions of significance in the right lateral hemisphere (p<0.05). The additive benefit mechanism was observed in the rostral middle frontal gyrus. Within groups differences were not observed in the insula, inerior parietal, and three regions of the superior parietal.

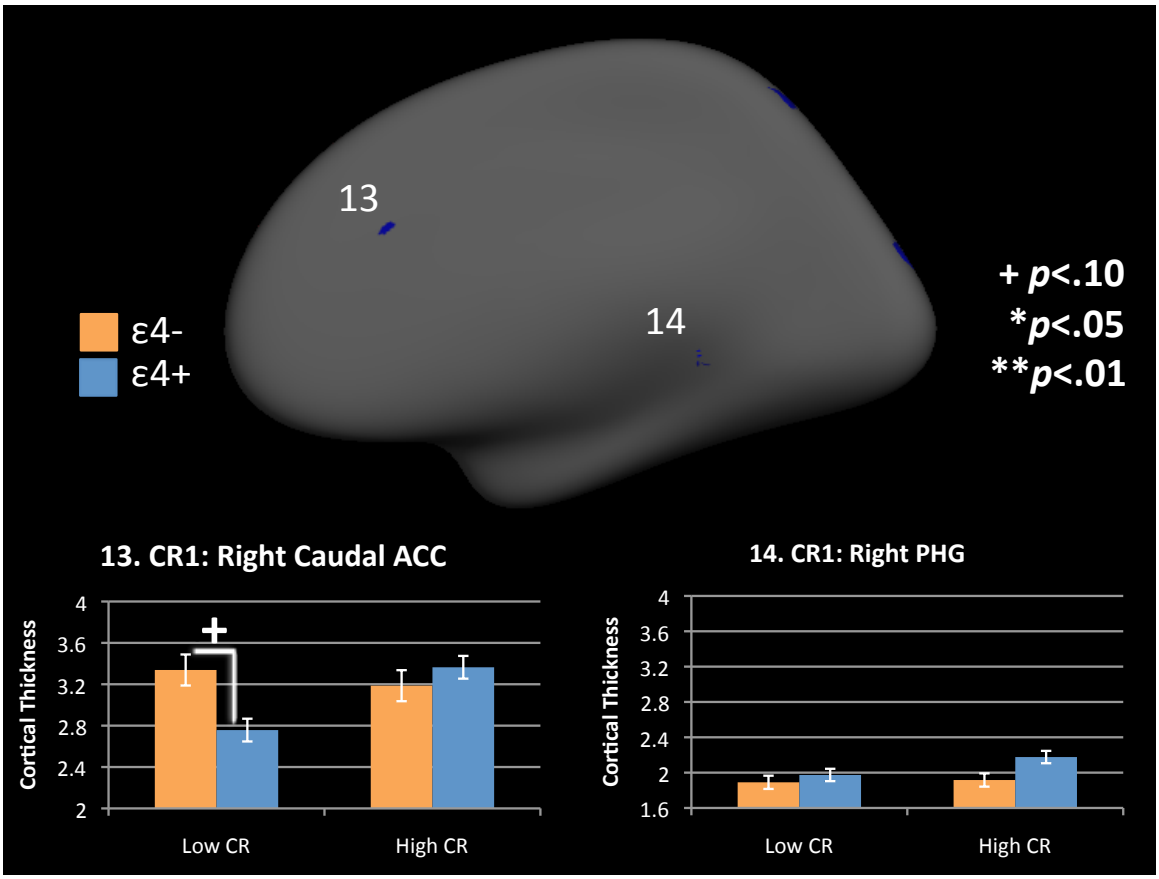


Figure 7: CR1 and ε4 interaction graphs with corresponding region of significance in the right medial hemisphere (p<0.05). A trend for the additive detriment mechanism was observed in the caudal anterior cingulate. Within groups differences were not observed in the parahippocampal gyrus.

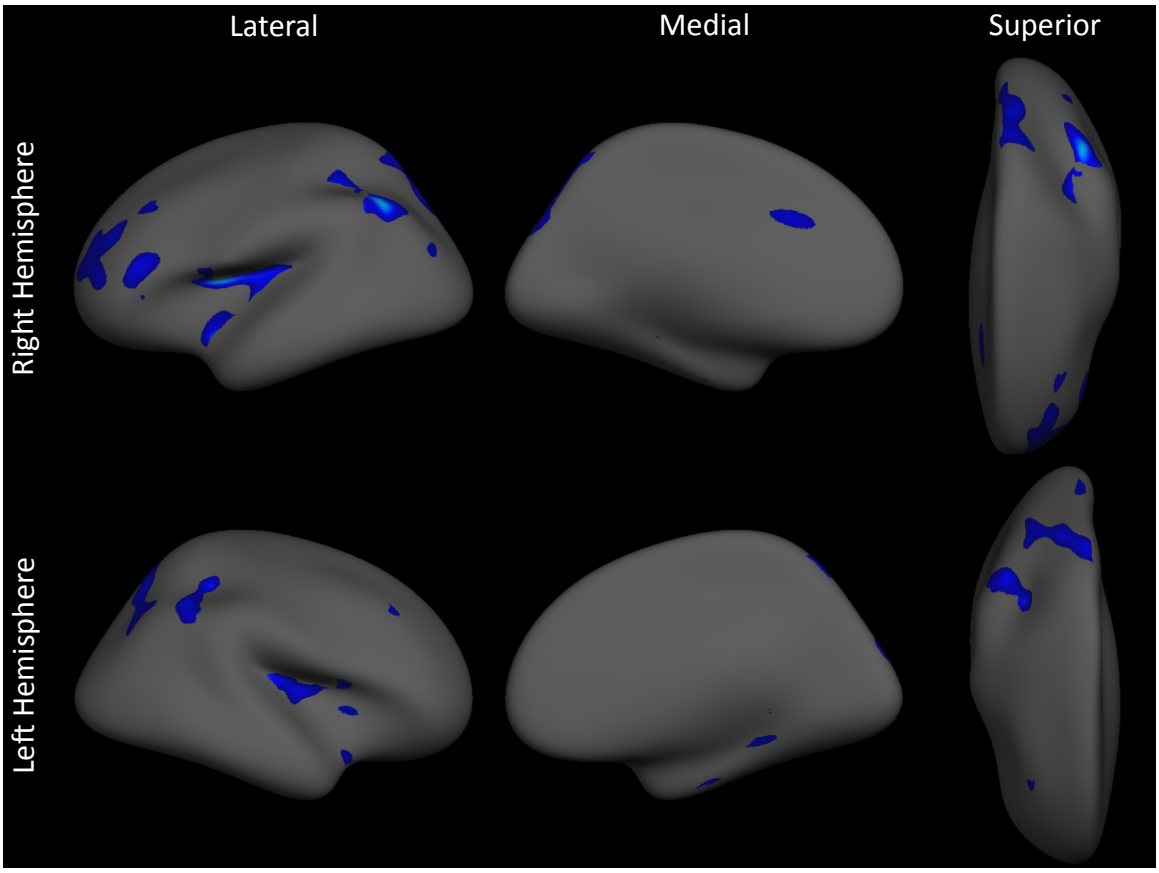


Figure 8: Results of bilateral CR2 vertex analysis. Blue regions show interactions between CR2 and ε4 (p<.0.05). Interactions were observed in bilateral rostral middle frontal gyri, insula, inferior and superior parietal regions, left anterior cingulate, and right parahippocampal gyrus.

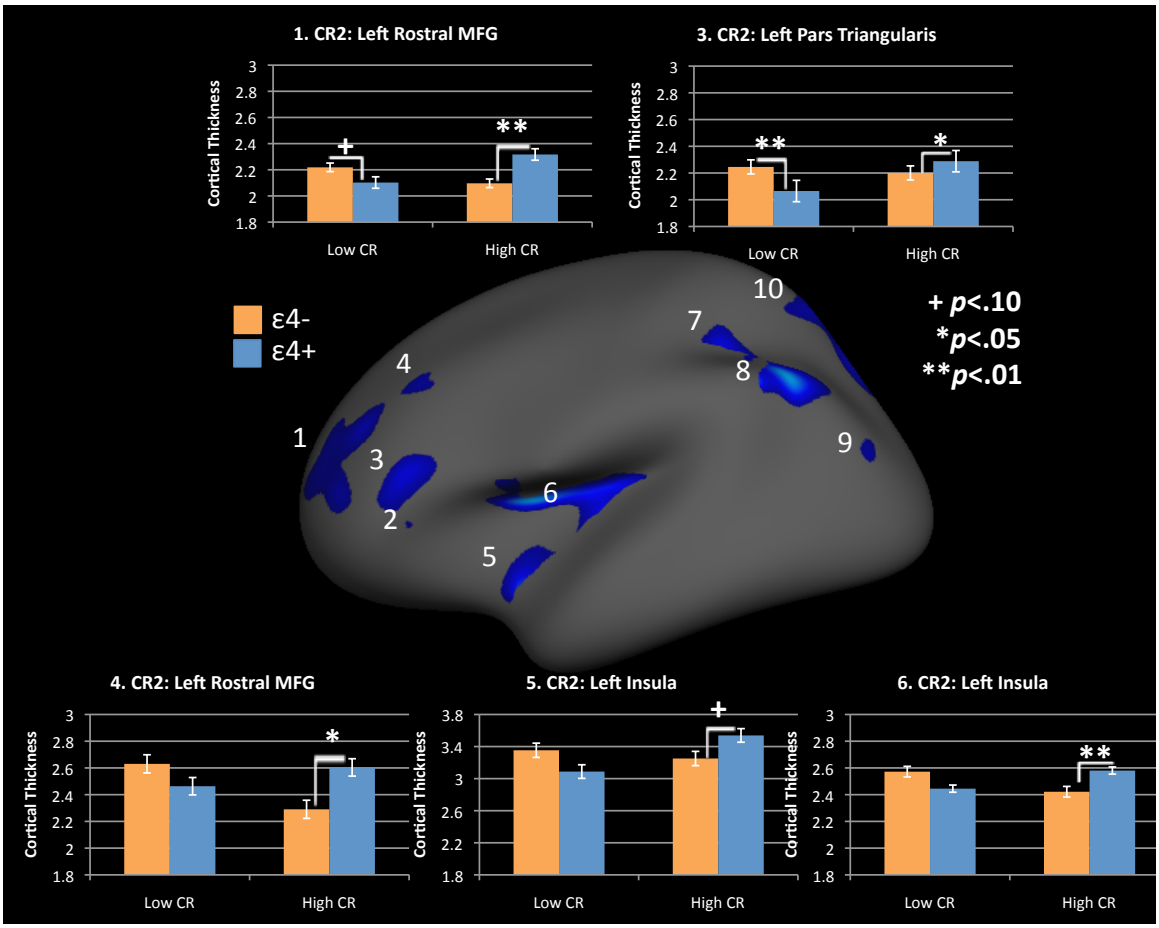
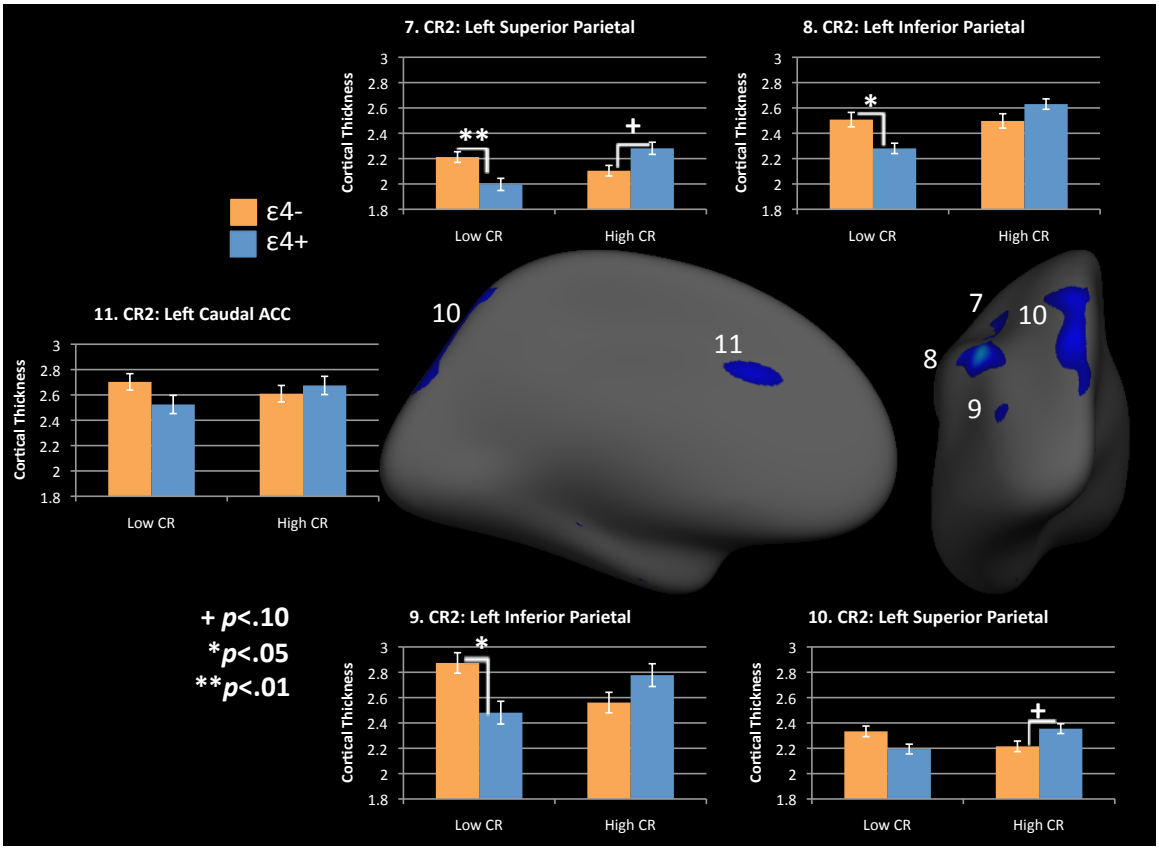


Figure 9: CR2 and ε4 interaction graphs with corresponding regions of significance in the left lateral hemisphere (p<0.05). The additive benefit mechanism was observed in the rostral middle frontal gyrus and two regions in the insula. Within groups differences were observed in both high and low CR in the rostral middle frontal gyrus and the left pars triangularis.



F*igure 10*: CR2 and ε4 interaction graphs with corresponding regions of significance in the left posterior and medial hemisphere (p<0.05). A statistical trend for the additive benefit mechanism was observed in one regions of the left superior parietal. The additive detriment mechanism was observed in a region of the inferior parietal lobule. Within groups differences in both high and low CR was observed in a region of the superior parietal. Finally, no within groups differences were found in a region of the caudal anterior cingulate cortex.

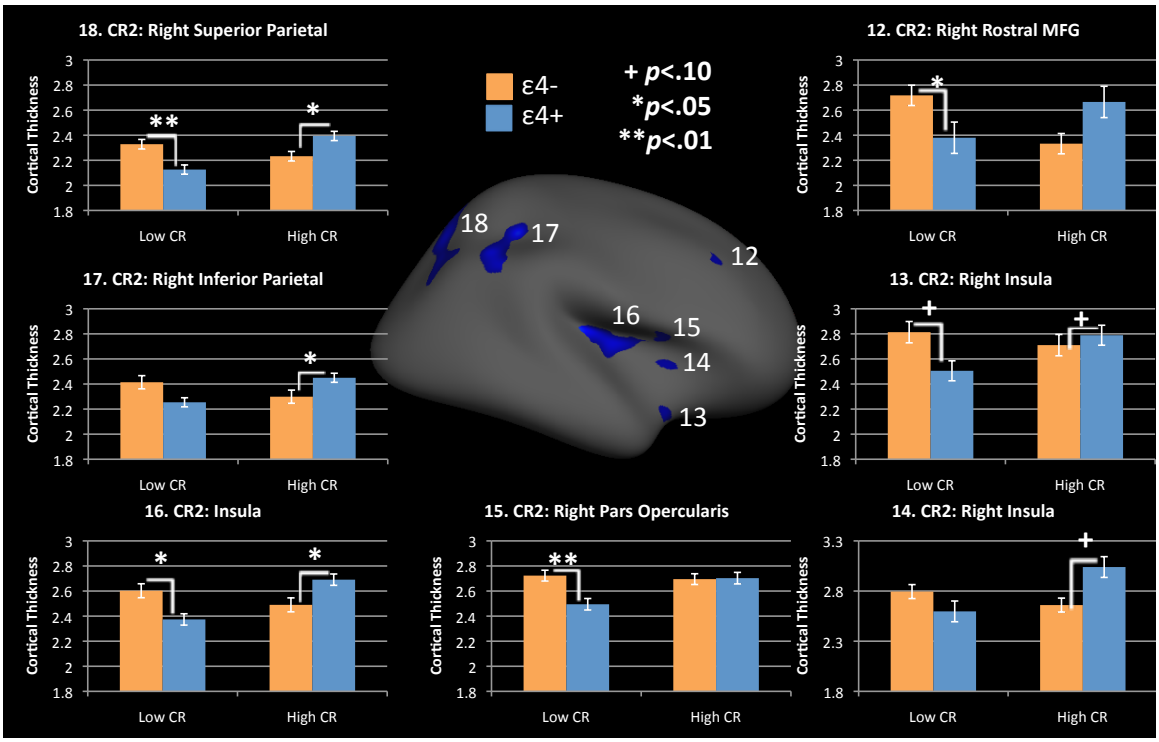


Figure 11: CR2 and ε4 interaction graphs with corresponding regions of significance in the right lateral hemisphere (p<0.05). The additive benefit mechanism was observed in the inferior parietal, and insula. The additive detriment mechanism was observed in the pars opercularis and rostral middle frontal gyrus. Within groups differences were observed in both high and low CR in the superior parietal and insula.

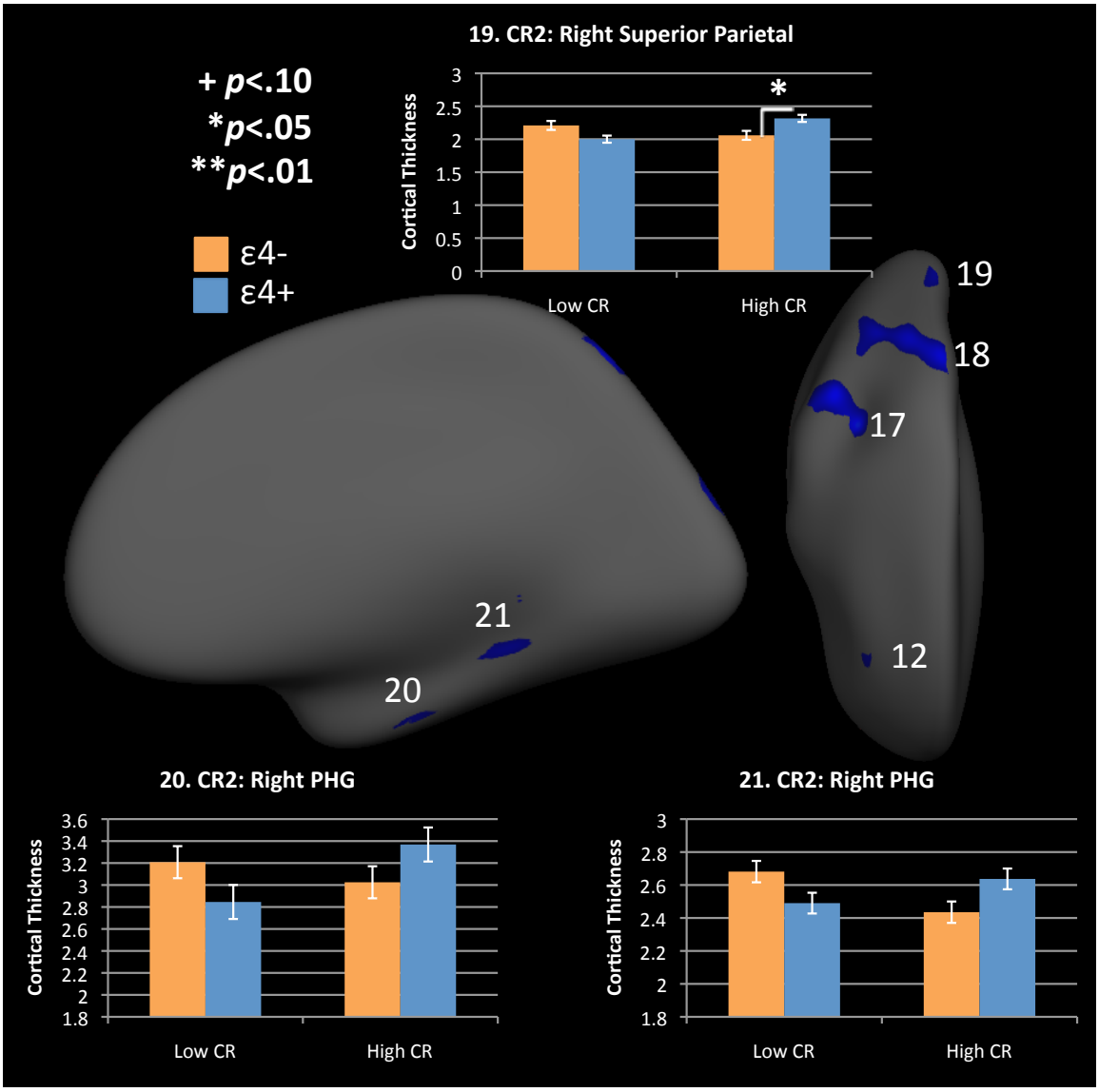


Figure 12: CR2 and ε4 interaction graphs with corresponding regions of significance in the right medial and posterior hemisphere (p<0.05). The additive benefit mechanism was observed in the superior parietal. Within groups differences were not observed in two regions in the parahippocampal gyrus.

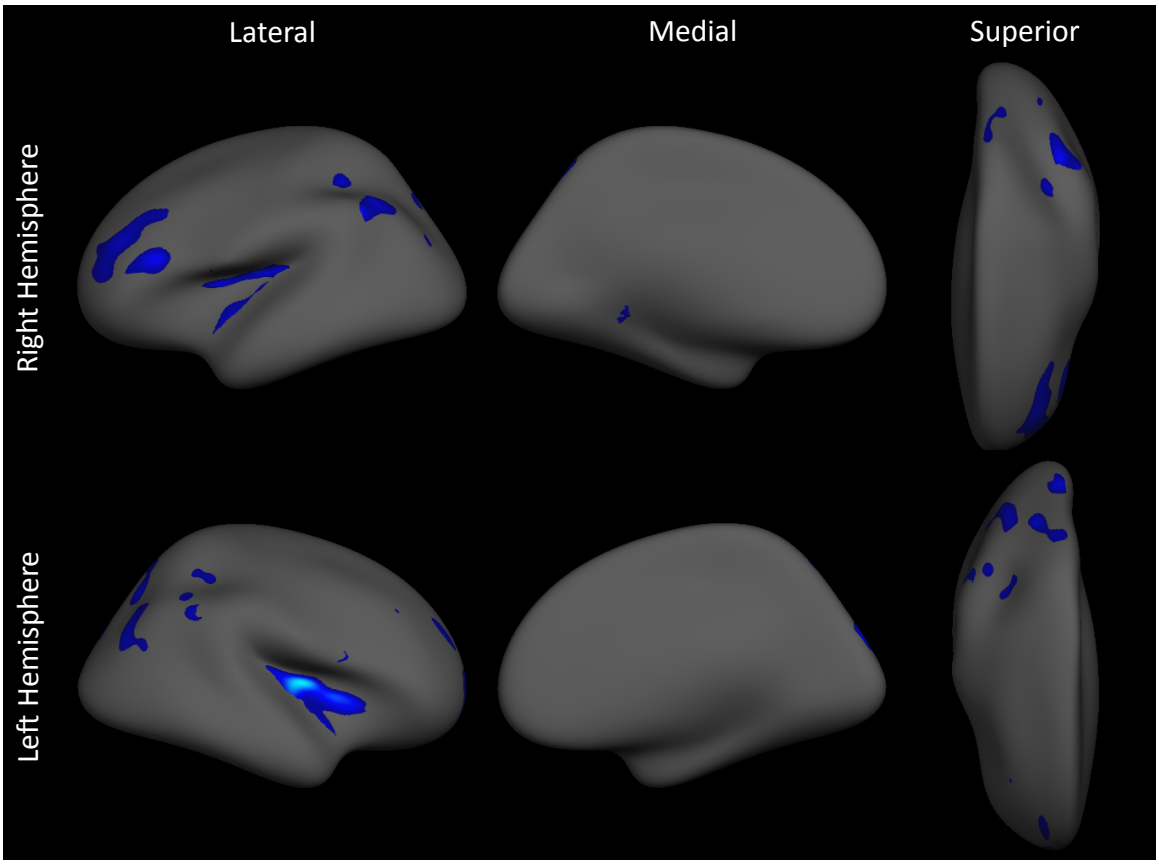


Figure 13. Results of bilateral CR3 vertex analysis. Blue regions show interactions between CR3 and ε4 (p<.0.05). Interactions were observed in bilateral rostral middle frontal gyri, inferior frontal gyri, insula, inferior and superior parietal regions, and left parahippocampal gyrus.

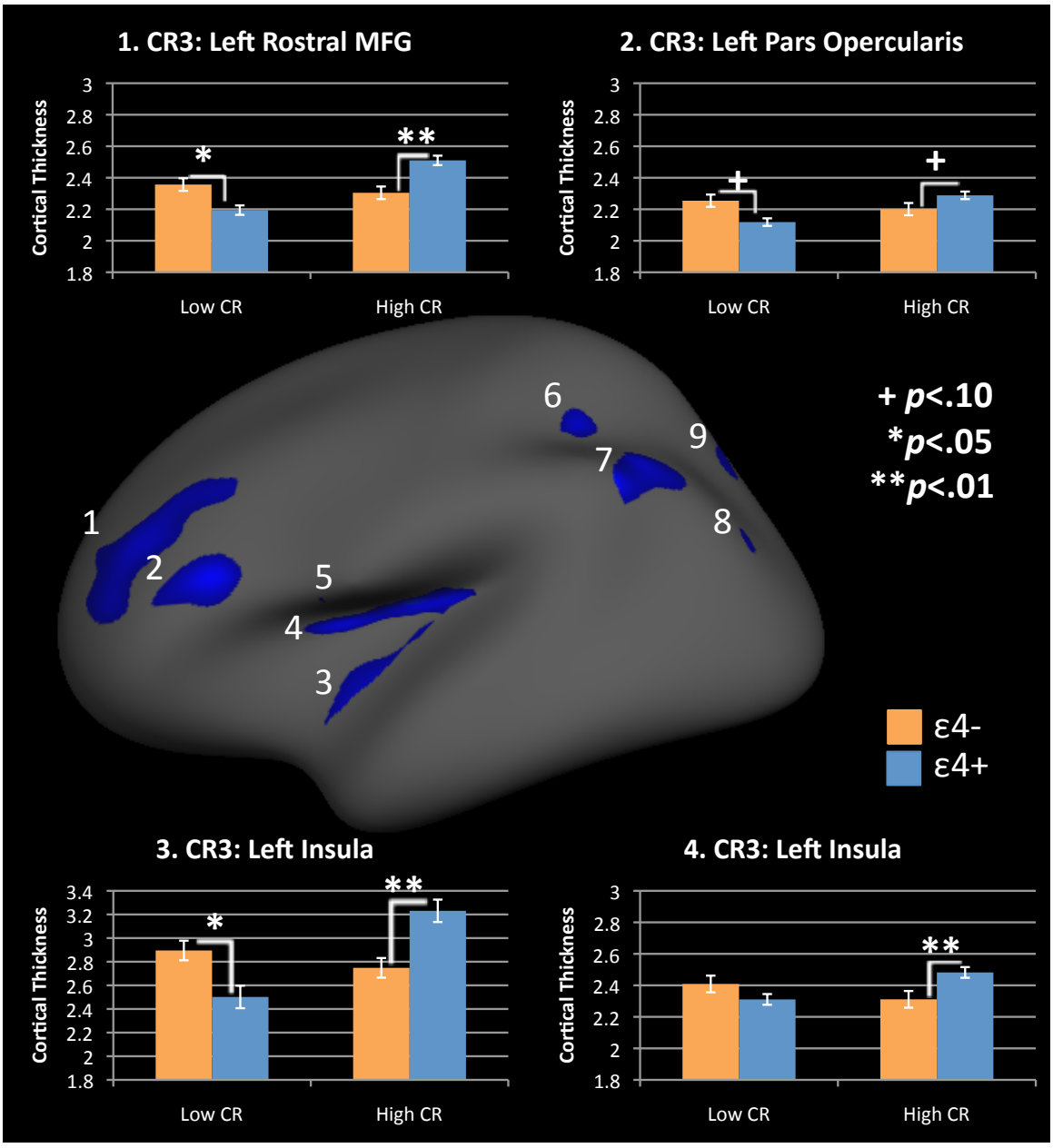


Figure 14: CR3 and ε4 interaction graphs with corresponding regions of significance in the left lateral hemisphere (p<0.05). The insula demonstrated the additive benefit mechanism. Within groups differences in both high and low CR were observed in regions of the rostral middle frontal gyrus, pars opercularis, and insula.

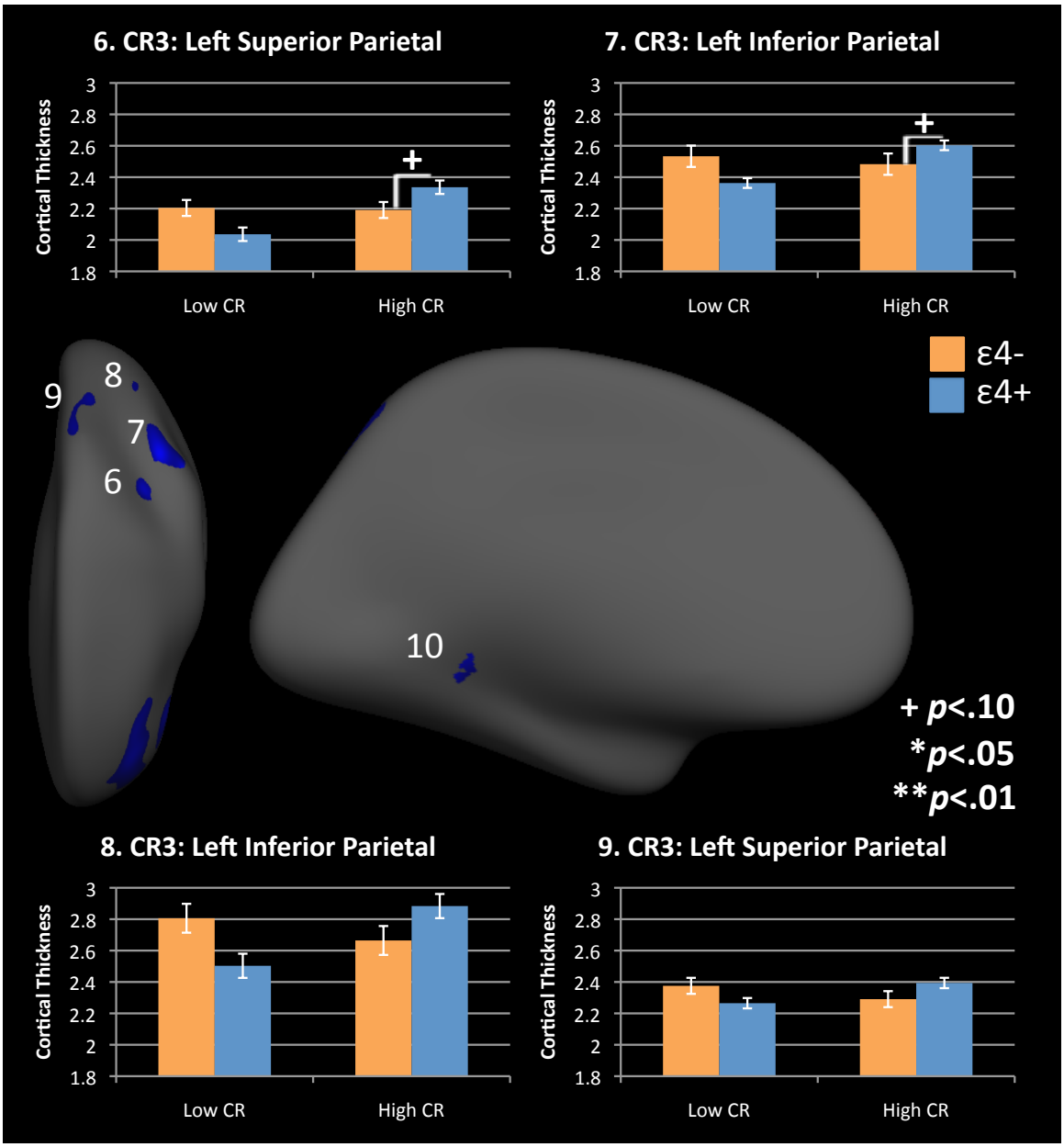


Figure 15: CR3 and ε4 interaction graphs with corresponding regions of significance in the left medial and posterior hemisphere (p<0.05). Trends for the added benefit mechanism was observed in the superior and inferior parietal regions. Two other regions in the inferior and superior parietal lobules did not demonstrate within groups differences in either high or low CR.

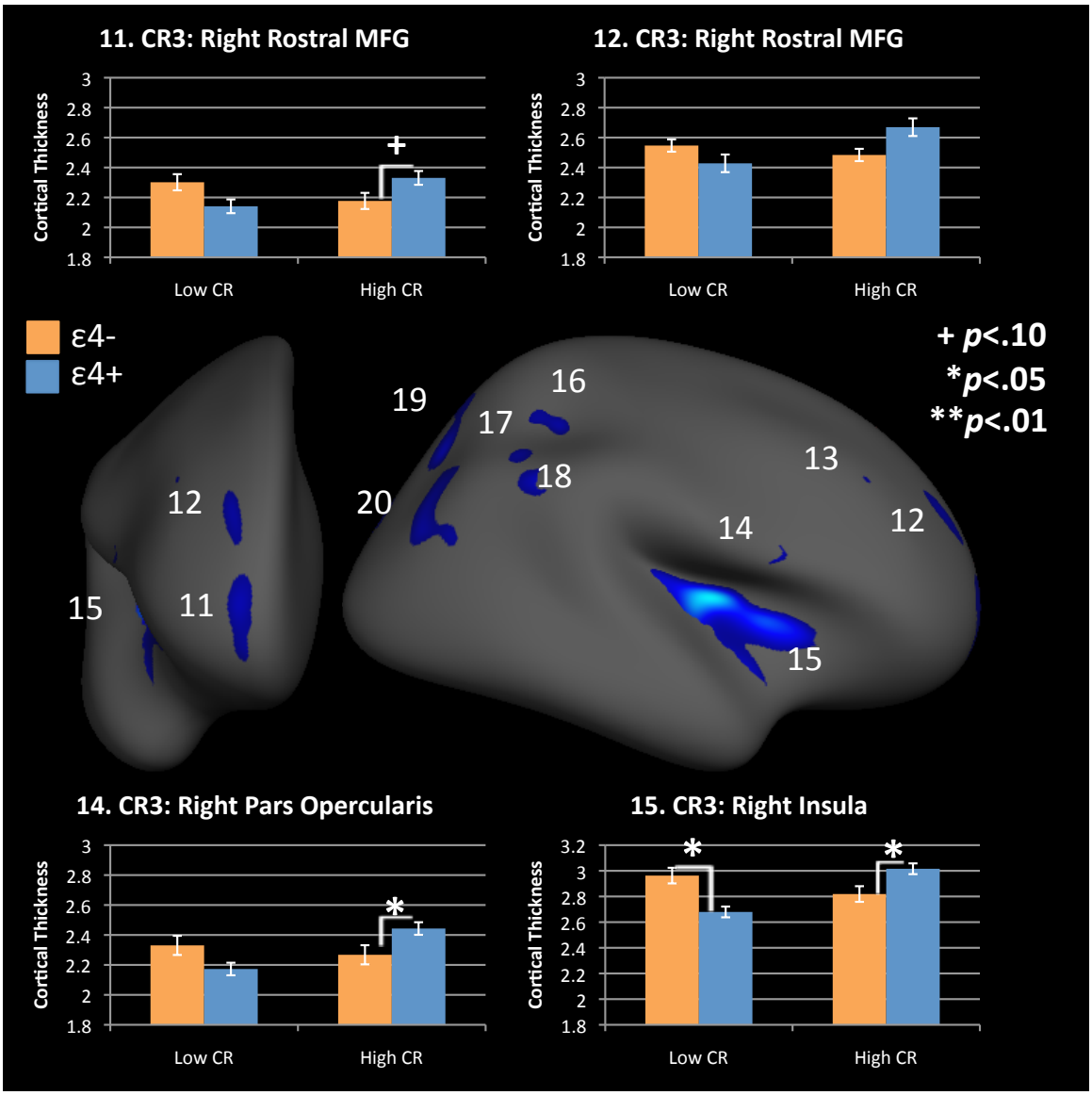


Figure 16: CR3 and ε4 interaction graphs with corresponding regions of significance in the right lateral hemisphere (p<0.05). The additive benefit mechanism was observed in the middle and inferior frontal gyri. A region in the insula showed within groups differences in both high and low CR groups. Another region in the middle frontal gyrus did not show within groups differences in high or low CR group

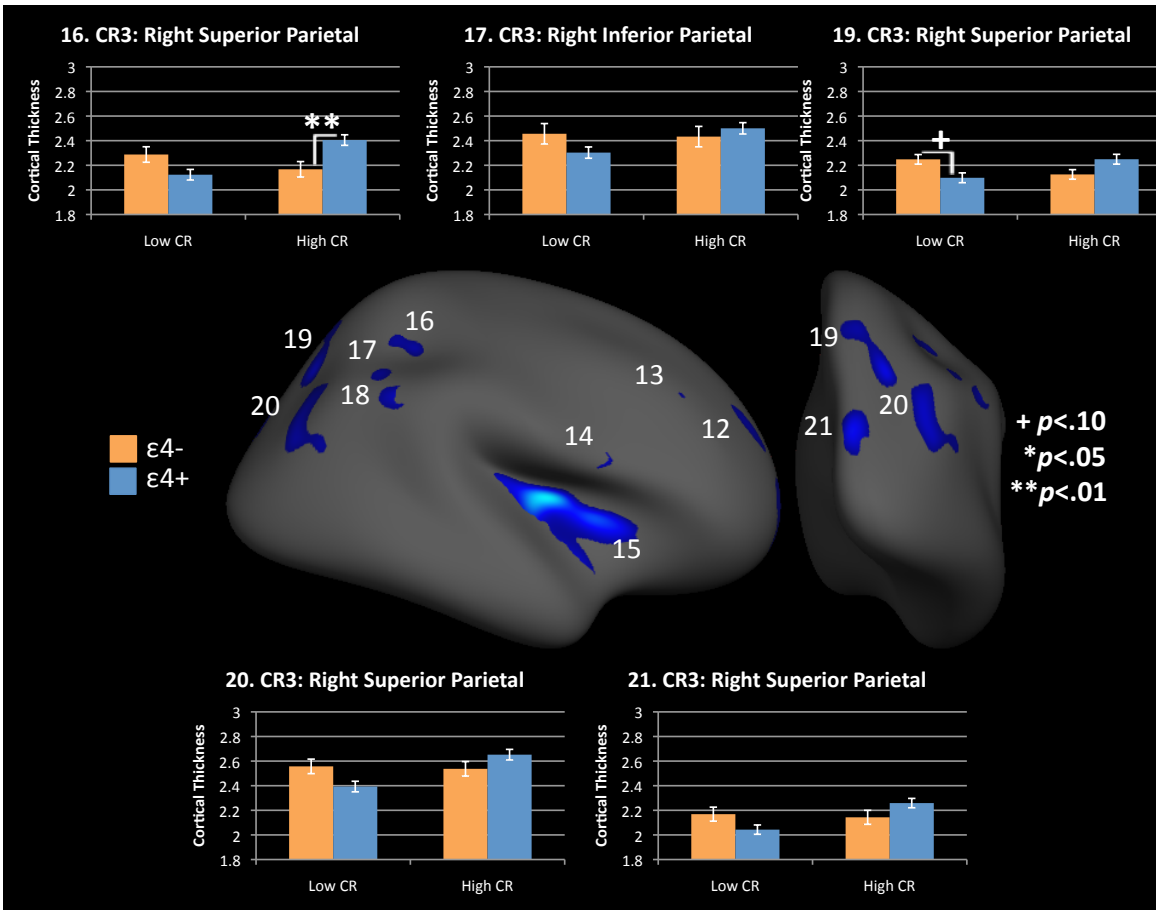


Figure 17: CR3 and ε4 interaction graphs with corresponding regions of significance in the right lateral and posterior hemisphere (p<0.05). The additive benefit mechanism was observed in a region in the superior parietal lobule. The additive detriment mechanism was observed in another region in the superior parietal. No within groups differences were observed in one region in the inferior parietal and two regions of the superior parietal lobule.