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# Genetic risk for Alzheimer's disease alters the five-year trajectory of semantic memory activation in cognitively intact elders

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ABSTRACT

Healthy aging is associated with cognitive declines typically accompanied by increased task-related brain activity in comparison to younger counterparts. The Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014) posits that compensatory brain processes are responsible for maintaining normal cognitive performance in older adults, despite accumulation of aging-related neural damage. Cross-sectional studies indicate that cognitively intact elders at genetic risk for Alzheimer's disease (AD) demonstrate patterns of increased brain activity compared to low risk elders, suggesting that compensation represents an early response to AD-associated pathology. Whether this compensatory response persists or declines with the onset of cognitive impairment can only be addressed using a longitudinal design. The current prospective, 5-year longitudinal study examined brain activation in APOE ε4 carriers (N = 24) and non-carriers (N = 21). All participants, ages 65–85 and cognitively intact at study entry, underwent task-activated fMRI, structural MRI, and neuropsychological assessments at baseline, 18, and 57 months. fMRI activation was measured in response to a semantic memory task requiring participants to discriminate famous from non-famous names. Results indicated that the trajectory of change in brain activation while performing this semantic memory task differed between APOE ε4 carriers and non-carriers. The APOE ε4 group exhibited greater activation than the Low Risk group at baseline, but they subsequently showed a progressive decline in activation during the follow-up periods with corresponding emergence of episodic memory loss and hippocampal atrophy. In contrast, the non-carriers demonstrated a gradual increase in activation over the 5-year period. Our results are consistent with the STAC model by demonstrating that compensation varies with the severity of underlying neural damage and can be exhausted with the onset of cognitive symptoms and increased structural brain pathology. Our fMRI results could not be attributed to changes in task performance, group differences in cerebral perfusion, or regional cortical atrophy.


## Introduction

Healthy aging is associated with mild and gradual declines in cognition functions, with the greatest aging-related changes involving memory, processing speed, and visuospatial skills (Salthouse, 2010). Such changes often occur in parallel with age-related alterations in brain structure, characterized by cortical atrophy and white matter abnormalities (Drachman, 2006; Kramer et al., 2007). Paradoxically, fMRI studies have consistently found *increased* regional brain activity in healthy elders relative to their younger counterparts during the performance of a cognitive task. This increased task-related brain activity in healthy elders typically occurs in brain regions also activated by younger participants, but can also be observed in homologous regions in the opposite hemisphere (Cabeza et al., 2002; Nielson et al., 2002, 2006). Some investigators have noted that age-related increases in brain activity occur most often in the frontal cortex; for reviews and discussion, see (Buckner, 2004; Eyler et al., 2011; Nielson et al., 2002). This increased neural activity is thought to serve as a compensatory function to support a high level of performance in older adults (Bangen et al., 2012; Carp et al., 2010; Grady, 2008; Han et al., 2009; Nielson et al., 2002, 2006; Prvulovic et al., 2005; Reuter-Lorenz and Cappell, 2008; Wierenga et al., 2008).

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**Table 1**
Baseline characteristics of Low Risk and APOE ε4 groups.

| Variable | Low Risk (n = 21) | APOE ε4 (n = 24) | p* | Cohen's d |
|---|---|---|---|---|
| MMSE | 29.29 (0.85)** | 29.21 (0.98) | 0.78 | 0.08 |
| DRS-2 memory | 24.29 (0.96) | 24.04 (1.60) | 0.53 | 0.18 |
| DRS-2 total | 141.05 (1.99) | 140.33 (3.60) | 0.41 | 0.24 |
| RAVLT delayed recall | 9.90 (2.14) | 9.75 (2.92) | 0.84 | 0.06 |
| RAVLT trials 1–5 | 49.33 (8.39) | 48.50 (8.17) | 0.74 | 0.10 |
| fMRI task | | | | |
| Famous (% correct) | 93.97 (5.23) | 91.39 (7.54) | 0.19 | 0.39 |
| Non-famous (% correct) | 95.87 (5.76) | 97.78 (3.63) | 0.20 | −0.40 |
| d′ | 3.29 (0.64) | 3.32 (0.62) | 0.85 | −0.06 |
| Famous (RT, msec) | 1236 (180) | 1249 (151) | 0.81 | −0.07 |
| Non-famous (RT, msec) | 1622 (354) | 1578 (358) | 0.68 | 0.13 |
| IIV famous (RT) | 351 (90) | 371 (131) | 0.57 | −0.17 |
| IIV non-famous (RT) | 347 (101) | 330 (94) | 0.56 | 0.18 |
| Hippocampal volume (% ICV) | 0.47 (0.06) | 0.46 (0.07) | 0.63 | 0.14 |

MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale-2; RAVLT = Rey Auditory Verbal Learning Test; RT = reaction time; IIV = intraindividual variability based on the average standard deviation of RTs for correct responses; % ICV = percent intracranial volume.
* p-Values derived from Student t-test, except for gender (Fischer's exact test).
** Mean (standard deviation).

One prominent theory, the Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009), posits that compensatory brain processes are responsible for preserving cognitive performance in older adults, despite accumulation of neural changes in the context of healthy aging (e.g., mild white matter disease, age-related atrophy). This theory identifies neural factors that contribute to maintenance of a specific level of cognitive function and does not address dynamic longitudinal changes occurring during the aging process. More recently, these authors (Reuter-Lorenz and Park, 2014) revised the STAC theory (STAC-r) to account for both positive (e.g., physical activity) and negative (e.g., presence of brain amyloid) factors that contribute to the rate of change in cognitive function during aging. This revision provides a framework for tracking the trajectory of neural compensation (scaffolding) in response to rate of change in cognitive processes, but empirical validation of the theory is dependent on imaging data derived from extended longitudinal imaging studies.

In the current prospective, 5-year longitudinal fMRI study, we examined compensatory neural scaffolding processes in cognitively intact elders at varying genetic risk for developing Alzheimer's disease (AD). The most important genetic risk factor for the sporadic form of AD (onset occurring after age 65) is the apolipoprotein E epsilon 4 (APOE ε4) allele (Farrer et al., 1997). Cross-sectional fMRI studies from our group (Seidenberg et al., 2009; Smith et al., 2011; Woodard et al., 2009, 2010) and others (Bookheimer et al., 2000; Borghesani et al., 2008; Filippini et al., 2011; Han et al., 2007; Trachtenberg et al., 2012; Wierenga and Bondi, 2007; Wierenga et al., 2010) have consistently demonstrated greater brain activation (neural scaffolding) in cognitively intact elders at higher genetic risk for AD (based on the presence of one or both APOE ε4 alleles and/or a family history of AD) than elders at lower genetic risk. Presumably, this increased activation occurs because the neuropathological changes associated with AD begin years or decades prior to symptom manifestation in persons at genetic risk for AD (Bateman et al., 2012; Jack et al., 2010). Indeed, alterations in task-related brain activity and cognitive performance have been reported in cross-sectional studies of APOE-ε4 positive individuals beginning in middle age and earlier (Evans et al., 2014; Reiman et al., 2004).

For this study, we recruited cognitively intact elders, APOE ε4 carriers and non-carriers, who underwent repeat cognitive testing, structural MRI, and task-activated fMRI on three occasions: study entry, 18 and 57 months. The fMRI task consisted of the Famous Name Recognition Task (FNRT) (Douville et al., 2005), a low-effort semantic memory task. The FNRT is performed with high accuracy even in patients with amnestic mild cognitive impairment (Woodard et al., 2009), thus removing high effort/low accuracy from complicating the interpretation of the longitudinal brain maps (Kennedy et al., 2014). Previous cross-sectional studies (Nielson et al., 2006, 2010; Seidenberg et al., 2009; Woodard et al., 2010) using this task have demonstrated a highly reproducible pattern of brain activation in regions that overlap with regions that comprise the "default-mode network" (Nielson et al., 2010; Sugarman et al., 2012).

Based on the STAC-r model, we hypothesized that the cognitively intact APOE ε4 carriers would exhibit greater task-related brain activation than non-carriers at study entry, presumably reflecting a compensatory response that may signal subsequent cognitive decline (Miller et al., 2008). Over time, however, a breakdown of neural scaffolding in the APOE ε4 carrier group is predicted to occur, characterized by the presence of age-inappropriate cognitive impairment. Decreased brain activity occurs in association with increased AD-related neural pathology (O'Brien et al., 2010) and is predicted to coincide with decreased episodic memory performance. Conversely, non-carriers, who maintain intact and stable episodic memory over the course of the 5 year follow-

**Table 2**
Coefficients from linear mixed effects analysis of neuropsychological test scores, fMRI task performance, and hippocampal volume.

| | Intercept (baseline) | | Slope (time) | |
|---|---|---|---|---|
| Variable | Low Risk[a] | APOE ε4 vs. Low Risk[b] | Low Risk[c] | APOE ε4 vs. Low Risk[d] |
| MMSE | 29.35 (0.18) | 0.014 (0.246) | 0.004 (.007) | −0.014 (.009) |
| DRS-2 memory | 24.30 (0.27) | −0.597 (0.367) | 0.008 (.008) | −0.019 (.011) |
| DRS-2 total | 140.19 (0.58) | −0.717 (0.790) | 0.007 (.016) | −0.019 (.022) |
| RAVLT delayed recall | 9.63 (0.56) | −0.397 (0.770) | 0.006 (.011) | ***−0.036 (.015)*** |
| RAVLT trials 1–5 | 48.84 (1.71) | −1.515 (2.339) | −0.005 (.032) | −0.028 (.044) |
| fMRI task | | | | |
| Famous (% correct) | 94.46 (1.27) | −2.479 (1.738) | −0.099 (0.054) | 0.026 (0.074) |
| Non-famous (% correct) | 96.91 (1.09) | 1.456 (1.498) | −0.113 (0.071) | −0.030 (0.097) |
| d′ | 3.38 (0.12) | −0.011 (0.162) | −0.007 (0.005) | −0.003 (0.006) |
| Famous (RT, msec) | 1248.0 (36.0) | −0.893 (49.339) | −1.034 (0.757) | 1.688 (1.046) |
| Non-famous (RT, msec) | 1628.1 (74.1) | −46.960 (101.430) | ***−3.425 (1.675)*** | 3.997 (2.304) |
| IIV famous (RT, msec) | 353.4 (23.0) | 10.622 (31.475) | −0.237 (0.408) | 0.532 (0.564) |
| IIV non-famous (RT, msec) | 338.3 (21.4) | −5.952 (29.308) | −0.438 (0.593) | 1.394 (0.817) |
| Hippocampal volume (% ICV) | 0.47 (0.01) | −0.0100 (0.0203) | −0.0001 (0.0001) | ***−0.0003 (0.0001)*** |

***Bolded*** values are statistically significant at p < 0.05.
MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale-2; RAVLT = Rey Auditory Verbal Learning Test; RT = reaction time; IIV = intraindivual variability based on the average standard deviation of RTs for correct responses; % ICV = percent intracranial volume.
[a] Predicted mean intercept (baseline) value of each dependent variable for the Low Risk group. All values are statistically significant from 0.
[b] Predicted difference between mean intercept (baseline) values for the Low Risk group and the APOE ε4 group.
[c] Predicted average monthly rate of change (slope) for the Low Risk group.
[d] Predicted difference in the average monthly rate of change (slope) between the Low Risk group and the APOE ε4 group. Standard errors of coefficients are in parentheses.