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Neuroimaging Markers Associated with Maintenance of Optimal Memory Performance in Late-Life

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Abstract

Background—Age-related memory decline has been well-documented; however, some individuals reach their 8th–10th decade while maintaining strong memory performance.

Objective—To determine which demographic and biomarker factors differentiated top memory performers (aged 75+, top 20% for memory) from their peers and whether top memory performance was maintained over 3 years.

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Methods—Clinically normal adults ($n = 125$, CDR = 0; age: 79.5 ± 3.57 years) from the Harvard Aging Brain Study underwent cognitive testing and neuroimaging (amyloid PET, MRI) at baseline and 3-year follow-up. Participants were grouped into Optimal ($n = 25$) vs. Typical ($n = 100$) performers using performance on 3 challenging memory measures. Non-parametric tests were used to compare groups.

Results—There were no differences in age, sex, or education between Optimal vs. Typical performers. The Optimal group performed better in Processing Speed ($p = 0.016$) and Executive Functioning ($p < 0.001$). Optimal performers had larger hippocampal volumes at baseline compared with Typical Performers ($p = 0.027$) but no differences in amyloid burden ($p = 0.442$). Twenty-three of the 25 Optimal performers had longitudinal data and 16 maintained top memory performance while 7 declined. Non-Maintainers additionally declined in Executive Functioning but not Processing Speed. Longitudinally, there were no hippocampal volume differences between Maintainers and Non-Maintainers, however Non-Maintainers exhibited higher amyloid burden at baseline in contrast with Maintainers ($p = 0.008$).

Conclusions—Excellent memory performance in late life does not guarantee protection against cognitive decline. Those who maintain an optimal memory into the 8th and 9th decades may have lower levels of AD pathology.

Keywords

memory; amyloid; SuperAging

1. Introduction

Age-related memory decline occurs throughout the life span (Evans et al., 2011; Salthouse, 2004) and is often considered an unavoidable aspect of “normal aging”. Despite these observations, there are documented cases of individuals who maintain excellent memory performance in later life (Harrison et al., 2012). Interestingly, many successful agers among the “oldest old” who continue to perform normally up until the time of their death have brain pathology that is indistinguishable from those with Alzheimer’s disease (AD) (Balasubramanian et al., 2012). This suggests that some individuals are more resilient to cognitive decline in the setting of AD pathology. However, there are more recent studies suggesting that SuperAgers have a lower frequency of the ApoE-4 allele and fewer surrogate markers for AD (Harrison et al., 2012; Rogalski et al., 2013). Furthermore, greater amyloid burden has been associated with cognitive decline in the oldest-old (age 90+) (Kawas et al., 2013; Snitz et al., 2013). Thus, it remains unclear to what extent optimal cognitive aging in late life reflects resilience to AD pathology or absence of AD pathology.

The advent of *in vivo* imaging of AD biomarkers, including amyloid Positron Emission Tomography (PET), allow for the examination of AD pathology in living individuals. We were interested in examining a subset of older individuals in the Harvard Aging Brain Study (HABS) who outperform their peers on memory measures to determine whether neuroimaging markers may be different from those with typical memory performance.

Multiple strategies have been used to operationalize optimal/successful aging, for example, characterizing according to physical functioning, self-reported ADLs, cognitive functioning, or life satisfaction (Depp & Jeste, 2006) as criteria for categorization. One particularly relevant example is SuperAging, which was originally defined as scoring 1) at or above a raw score of 9 on the delayed recall portion of the RAVLT and 2) performing at or above 1 SD average performance for age and education on non-memory measures according to published norms (Rogalski et al., 2013). Though not quite SuperAgers by definition, our Optimal Memory Performers consisted of a group of high functioning older adults aged 75+ who were performing in the top 20% on particularly challenging memory tests as compared to the remainder of the HABS sample. We compared the Optimal Memory Performers to their normally performing peers: Typical Memory Performers. We aimed to investigate whether the Optimal Memory Performers were less likely to be on the AD trajectory compared to their peers. In particular, we explored group differences in demographic, biomarker, and cognitive factors at baseline. We additionally examined Optimal Memory Performers who maintained their excellent performance at 3-year follow-up ($n = 16$) and those who declined ($n = 7$).

We hypothesized that Optimal Memory Performers may reflect a younger cohort within the 75+ range and may exhibit higher levels of education and higher socio-economic status given that these characteristics have been shown to be protective against cognitive decline (Karp et al., 2004; Scarmeas & Stern, 2003; Stern et al., 2012). Additionally, if Optimal Memory Performers are less at-risk for AD, we hypothesized that they would be more likely ApoE-4 allele non-carriers (Saunders et al., 1993) and exhibit lower amyloid-PET burden. They may additionally exhibit resilience to age-associated hippocampal atrophy (Mungas et al., 2005; Schuff et al., 2009). Finally, we were interested in whether optimal memory performance was mirrored in other cognitive domains, such as executive functioning and speed of processing. Better executive functioning may be associated with better performance on memory tasks, particularly challenging tasks that benefit from strategy development (Buckner, 2004; Grober et al., 2008).

2. Materials and Methods

2.1. Participants

Our sample consisted of 125 older adults (age: 79.5 ± 3.57 years, years of education: 15.54 ± 3.12 , MMSE: 28.79 ± 1.07 , 45% male) enrolled in the Harvard Aging Brain Study using previously described methods (Dagley et al., 2015) at the Massachusetts General Hospital. All participants signed an informed consent and the Partners Human Research Committee approved the study.

All participants were deemed clinically normal based on the (1) Mini Mental State Exam (MMSE) score (adjusted for age & education) (Folstein, Folstein, & McHugh, 1975), (2) scores above age and education adjusted cut-offs on the delayed paragraph recall (Logical Memory II) of the Wechsler Memory Scale-Revised (Wechsler, 1987), and (3) a Clinical Dementia Rating (CDR) (Morris, 1993) score of 0, as assessed by an experienced clinician. In addition, the American National Reading Test (AmNART) was used to derive an estimate of Verbal IQ with greater scores associated with higher intelligence (Paolo & Ryan, 1992).

Clinical and neurological exams confirmed that participants had no history of alcoholism or drug abuse in the last two years, head trauma, or current serious medical or psychiatric illness. Participants were only included in this analysis if they were 75 years of age and older and had completed neuropsychological testing, structural MRI, amyloid PET scans and ApoE genotyping.

2.2. Neuropsychological Evaluation

The memory composite score was composed of outcomes from the Memory Capacity Test (MCT) (Papp et al., 2015; Rentz et al., 2010), the Face Name Associative Memory Exam (FNAME) (Amariglio et al., 2012; Rentz et al., 2011), and the 6-trial Selective Reminding Test (SRT) (Masur et al., 1989). These tests were chosen because they are cognitively challenging and have been shown to be sensitive markers of amyloid deposition in high functioning individuals (Papp et al., 2015; Rentz et al., 2010). Two outcomes for each measure (delayed free-recall and delayed cued recall for MCT, delayed recall of names and occupations on the FNAME, and delayed recall and delayed multiple choice on the SRT) were z-transformed (using the mean and standard deviation of the whole HABS sample at baseline). The mean of these z-scores constituted the memory performance composite score. Participants were separated into two groups based on their memory composite score with high performers scoring in the top 20% ($n = 25$; performing > 0.5 SD above the mean), and typical performers scoring < 0.5 z-scores ($n = 100$). Three-year follow-up data was available on 23 of the original 25 Optimal Memory Performers. Based on their follow-up performance, participants were grouped into Optimal Maintainers and Optimal Non-Maintainers, described in detail in the Results section.

2.2.1. Executive Functioning and Speed of Processing—Previously validated factor scores from the HABS cohort were used for analysis of Executive Functions and Speeded Processing (Hedden et al., 2012). The Executive function score included the sum of words for letter fluency (F-A-S) produced in 60 seconds (Benton et al., 1983) production of animals, fruits and vegetables in 60 seconds (Monsch et al., 1992), Letter-Number sequencing of the Wechsler Scale-III (Wechsler, 1997), Digit Span Backward (adapted from Petrides and Milner, 1982 and Shimamura and Jurica, 1994), a switching score from the Number-Letter task (adapted from Miyake et al., 2000 and Rogers and Monsell, 1995), the Flanker test (adapted from Eriksen and Eriksen, 1974 and Ridderinkhof et al., 1999) and Trail Making Test B minus A (Reitan, 1979). Processing Speed consisted of the Number Letter non-switching task, Trail Making Test A, and the Digit Symbol subtest of WAIS-R (Wechsler, 1981).

2.3. Biomarkers

2.3.1. Structural MRI data acquisition and analysis—MRI was completed on a Siemens Trio-TIM 3T scanner with a 12-channel phased-array whole-head coil. Structural T1 weighted images were acquired as magnetization-prepared rapid gradient-echo (MPRAGE) with the following acquisition parameters: TR/TE/TI = 2300/2.95/900ms, flip angle = 9° , 1.1x1.1x1.2mm resolution, 2X (GRAPPA) acceleration. Hippocampal volumes were collapsed across hemispheres and intracranial volume (ICV) controlled using: raw HV — b (ICV — mean ICV), b = unstandardized coefficient when HV is regressed against ICV.

Region of interest labeling was derived using FreeSurfer v5.1 (Fischl, 2012). MRI was collected at baseline and 3-year follow-up.

2.3.2. PET data acquisition and analysis—PET imaging was completed at the MGH PET facility. Fibrillar amyloid binding was measured with the radiotracer Pittsburgh Compound B-PiB (Klunk et al., 2004; Mathis et al., 2003) using a Siemens ECAT EXACT HR+ PET scanner. After injection of 8.5–15 mCi PiB, 60-mins of dynamic data were acquired in 3D acquisition mode. PiB data were analyzed using the distribution volume ratio (DVR) created using the Logan graphical analysis method with cerebellar cortex as reference tissue (Logan et al., 1996; Price et al., 2005). PiB PET was collected at baseline and 3-year follow-up.

2.3.3. ApoE e4 Status—Blood samples were collected from all the participants using standard procedures to evaluate ApoE polymorphisms. Participants were categorized as carriers and non-carriers based on whether or not they carried the e4 allele.

2.4. Statistical Analyses

Two sets of analyses were conducted with baseline data: differences between (1) Optimal Memory Performers and Typical Memory Performers and (2) Optimal Maintainers and Optimal Non-Maintainers. Non-parametric measures (i.e., Mann-Whitney U Test) were used to compare groups to account for the disproportionate sample size at baseline and reduced sample size when examining the Optimal Maintainers vs. Non-Maintainers. Differences in sex and e4 status (+/–) between groups were determined using Fisher's Exact Test (2-sided). To determine whether Optimal Maintainers vs. Non-Maintainers declined in Processing Speed or Executive Functioning, exhibited more amyloid accumulation or reduced hippocampal volume over 3 years, change scores were calculated and Mann-Whitney U Tests were used to determine whether there were significant differences between groups.

3. Results

3.1. Differences Between Optimal Memory Performers and Typical Memory Performers

3.1.1. Demographic Factors—There were no significant group differences between Optimal Memory Performers ($n = 25$) vs. Typical Memory Performers ($n = 100$) in terms of age, educational attainment, estimated verbal intelligence, or in distribution of sex (Table 1) at baseline. However, Optimal Memory Performers scored significantly higher on the baseline cognitive screening measures including the MMSE ($U = 1610$, $z = 2.34$, $p = 0.02$) and Logical Memory delayed recall ($U = 1640$, $z = 2.62$, $p = 0.009$) compared with Typical Memory Performers.

3.1.2. Biomarker Factors—At baseline, Optimal Memory Performers had significantly larger hippocampal volumes compared with the Typical Memory Performers ($p = 0.027$) (Table 1, Figure 2). In the combined sample of Optimal and Typical memory performers with longitudinal hippocampal volume ($n = 83$), there was no differential rate of atrophy between groups ($U = 516$, $z = -0.99$, $p = 0.319$) with Optimal and Typical performers losing volume equivalently.

There were no significant group differences in level of amyloid burden between the Optimal and Typical groups ($p = 0.442$). A total of 16% of the Optimal Memory Performers were $\epsilon 4$ carriers compared with 30% of the Typical Performers, however this difference was not significant ($p = 0.209$).

3.1.3. Cognitive Factors—At baseline, Optimal Memory Performers outperformed Typical Memory Performers on both composites of Executive Functioning ($p < 0.001$) as well as Processing Speed ($p = 0.016$) (Table 1).

3.2. Longitudinal Trajectories of the Optimal Memory Performers

Follow-up data on the original 25 Optimal Memory Performers revealed a nonsignificant trend for memory decline at the group level, $z = -1.89$ $p = 0.059$ (Figure 1). A total of 16 individuals maintained their optimal status (Maintainers) by continuing to perform 0.5 SD above the mean for the Memory Composite while 7 declined compared with their initial performance (Non-Maintainers). Two Optimal Memory Performers did not have follow-up data because they discontinued study participation. Of the 23 initial optimal performers with follow-up cognitive data, 19 had biomarker data for longitudinal PiB PET and hippocampal volume (2 discontinued participation in the imaging portion of the study because of medical restrictions).

3.2.1. Demographic Factors—There were no demographic differences (i.e., sex, age, education, or estimated verbal IQ) between Optimal Maintainers ($n = 16$) versus Optimal Non-Maintainers ($n = 7$) (Table 2).

3.2.2. Biomarker Factors—Unlike baseline group differences in hippocampal volume observed between the Optimal and Typical groups, there was no difference in baseline hippocampal volume between Optimal Maintainers vs. Non-Maintainers (Table 2, Figure 2). There was no difference in hippocampal atrophy over 3 years between Maintainers and Non-Maintainers, $U = 42$, $z = -0.23$, $p = 0.850$ (Figure 2).

Optimal Memory Maintainers exhibited lower amyloid burden at baseline compared with Non-Maintainers ($p = 0.008$). Non-Maintainers did not accumulate amyloid at a faster rate compared with the Maintainers, $U = 22$, $z = -1.20$, $p = 0.257$ (Figure 3). There were no group differences in $\epsilon 4$ carriage between Maintainers and Non-Maintainers (Table 2).

3.2.3. Cognitive Factors—Unlike lower performance in Executive Functioning and Processing Speed observed in Typical vs. Optimal performers at baseline, there were no group differences in performance in these non-memory domains between Optimal Maintainers versus Non-Maintainers at baseline (Table 2). Optimal Non-Maintainers exhibited greater decline in Executive Functioning over time compared with the Optimal Maintainers, $U = 100$, $z = 2.94$, $p = 0.002$ (Figure 4). However, there were no group differences in Processing Speed over time, $U = 66$, $z = 0.67$, $p = 0.535$ (Figure 4).

4. Discussion

Our finding that Optimal Memory Performers had larger hippocampal volumes compared with their Typically-performing peers is consistent with recent work showing that SuperAgers exhibit more “youthful” paralimbic and limbic structures (Sun et al., 2016) and less age-related cortical atrophy (Harrison et al., 2012). While there was no association between Optimal vs. Typical performance and amyloid burden cross-sectionally, maintenance of optimal memory performance over 3 years was associated with lower amyloid burden at baseline. Combined, these findings support the notion that while excellent memory performance in late life may be associated with more robust memory-related anatomy, reduced evidence for Alzheimer’s risk markers is only associated with *maintenance* of that optimal memory performance. Thus, simply possessing optimal memory performance in late life does not guarantee a continued benign cognitive aging trajectory.

The lack of a difference in cross-sectional amyloid burden between Optimal and Typical Performers is not surprising. Growing evidence suggests that the cross-sectional relationship between amyloid burden and cognition in clinically normal older adults is somewhat tenuous (Hedden et al., 2013; Mormino et al., 2014). This is consistent with the hypothetical model of Alzheimer’s disease whereby amyloid accumulation represents an early precipitating event (Sperling et al., 2011) that initiates a cascade leading to neuronal injury and subsequent cognitive decline. Our finding that lower amyloid burden at baseline was associated with maintenance of optimal memory performance over 3 years is consistent with this hypothetical model. More specifically, optimal non-maintainers may represent a group that is progressing on the preclinical trajectory compared with Maintainers. It is important to note, however, that only 2 of the 7 “non-maintainers” declined more than one standard deviation below the sample mean. Additionally, Evans et al. (2011) noted that even if two 80 year olds get the same score on a memory measure, one may be declining, while the other is not. This is why it is imperative to collect longitudinal follow-up data even on those who are deemed Optimal Memory Performers at baseline in order to determine whether non-maintenance of optimal memory has clinically meaningful repercussions.

Previous work observing SuperAgers over 1.5 years showed stability of cognitive performance over that time frame (Gefen et al., 2014). This discrepancy in findings between our Optimal Memory Performers and previously reported SuperAgers is likely influenced by different selection criteria and measures employed, as well as different follow-up periods. We used multiple challenging memory measures to define our Optimal and Typical Performers in order to fully capture excellent memory performance across a range of memory tests. Within a challenging memory composite, the Optimal Memory Performers scored at or above 0.5 SDs on the memory composite score with the highest performer scoring only 1.2 SDs above the mean. This more limited range in performance is consistent with a highly educated and high functioning cohort. We employed the 0.5 SD cut-off rather than comparing performance to normative data, because of the unavailability of normative data on two of the challenging memory tests. Despite the sampling differences between the two studies, the 3-year longitudinal follow up of our Optimal Performers

suggests that over this time frame, not everyone will retain their high performance, whereas stability of performance may be maintained over a shorter time frame.

While our Optimal performers exhibited larger hippocampal volumes, it remains unclear whether larger hippocampal volumes in Optimal Memory Performers reflect a developmental advantage (i.e., they always had larger hippocampi) or resilience to age-related hippocampal atrophy. Hippocampal atrophy has multiple etiologies including pathologic TDP43 (Josephs et al., 2015) and cerebrovascular disease (Mungas et al., 2002) in addition to AD.

The lack of a difference between groups and carriage of the ApoE-4 allele is not entirely surprising given that the peak effect of $\epsilon 4$ seems to occur for those in their 60s, and that a majority of $\epsilon 4$ carriers demonstrate clinical progression to MCI or AD dementia prior to 75 years of age (Blackner & Tanzi, 1998; Caselli et al., 2009). Thus, it is likely that $\epsilon 4$ carriers who are over 75 years of age and remain clinically normal may not be representative of the $\epsilon 4$ carrier population at large. The small number of individuals belonging to this group ($n = 4$) limits their characterization.

The Optimal Memory Performers were initially defined by their performance on highly challenging tasks of memory but they also outperformed their Typical peers on measures of executive function and speed of processing. It is likely that the Optimal group's superior memory performance could be reflected by strengths in other cognitive domains, such as executive functions and processing speed. The memory measures used to define Optimal Agers are particularly challenging, and good attention and strategic skills are required to bolster performance (Buckner, 2004). Optimal Non-Maintainers declined at a faster rate in Executive Functioning compared with the Maintainers. This suggests that decline among initially Optimal Memory Performers is not necessarily specific to the memory domain.

A limitation of this study is the small sample size. We selected the top 20% cut-off for Optimal Memory Performers to maximize our sample size rather than examining only the top SuperAgers. Despite the small sample, we believe that this finding contributes to the field, and aligns with other studies, which also report small sample sizes (Rogalski et al., 2013). Our cohort consists of very high functioning individuals for their age who were selected based on normal cognition and therefore may not be representative of the young elderly or oldest old population at large. Furthermore, individuals who reach age 75+ while remaining cognitively normal may, by definition, have particularly robust brain health. Survival bias may also play a role in the lack of differences in cognitive reserve (i.e., educational achievement, estimated IQ) observed between groups. Previous studies showing protective effects of high educational achievement and cognitive engagement had a much wider array of educational and socioeconomic statuses in their samples (Koster et al., 2005).

In sum, greater hippocampal volumes at the cross-section contributed to optimal memory performance at age 75+, however, maintenance of that excellent performance over 3 years was associated with lower amyloid burden suggesting that 1) excellent memory performance in late life does not guarantee protection against cognitive decline, and 2) those who remain cognitively optimal over time may have less AD-specific pathology. These findings also

speak to the larger question of the concept of “normal aging.” Observational studies consistently observe a negative correlation between cognitive performance across multiple domains and age (Hedden, 2004; Salthouse, 2004) and neuropsychologists rely on age-corrected normative data to identify “normal” versus worrisome cognitive decline. Previous SuperAger findings combined with our own finding of biomarker differences among Optimal versus Typical Memory Performers and Optimal Maintainers versus Non-Maintainers suggests that a certain proportion of what is considered “normal age-related decline” is in fact potentially pathological. *In vivo* imaging of amyloid and more recently tau, provides an unprecedented opportunity to improve normative data by incorporating biomarker-corrected normative data (Hassenstab et al., 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Optimal Memory Performance is associated with larger baseline hippocampal volumes.
- Optimal Memory retention is associated with lower baseline amyloid levels.
- There were no demographic differences between Optimal and Typical Performers.

Figure 1. Optimal Memory Performance over Time

Memory composites scores at baseline for Optimal Memory Performers ($n = 25$) and 3-year follow-up showing Optimal Maintainers ($n = 15$, scoring > 0.5 SD's above the mean) and Optimal Non-Maintainers ($n = 7$).

Figure 2. Hippocampal Volume by Group

At baseline, Optimal Memory Performers ($n = 25$) exhibited larger hippocampal volumes compared with Typical Memory Performers ($n = 100$). Both Optimal Maintainers ($n = 16$) and Non-Maintainers ($n = 7$) exhibited hippocampal atrophy over 3 years; however, rates of decline did not differ between groups.

Figure 3. Amyloid PET Deposition by Group

There was no difference in amyloid burden between Optimal and Typical Memory Performers at Baseline. Optimal Non-Maintainers exhibited higher levels of amyloid burden at baseline and follow-up compared with Optimal Maintainers.

Figure 4. Non-Memory Cognitive Decline in Optimal Maintainers versus Non-Maintainers
Optimal Non-Maintainers exhibited greater decline in Executive Functions longitudinally (right) compared with Optimal Maintainers. No group differences were observed in Processing Speed (left).

Table 1

Group Differences between Optimal Aged and Typical Aged at Baseline.

	Optimal Performers (n = 25) Mdn (IQR)	Typical Performers (n = 100) Mdn (IQR)	Significance Testing	p-value
Demographic				
Age (yrs)	77.5(6.75)	78.89 (5.5)	U= 1061, z = -1.17	0.242
Sex (M/F)	9/16	47/53		0.374
Education (yrs)	16 (6)	16 (5)	U=1298, z = 0.30	0.762
Verbal IQ	125 (11)	124 (13)	U=1500, z = 1.64	0.101
Biomarkers				
Amyloid-PET(DVR)	1.16(0.29)	1.11 (0.25)	U=1375, z = 0.77	0.442
Hipp. Vol. (mm ³)	7293(750)	6883 (1190)	U=1546, z = 2.21	0.027 *
ApoE-4 (+/-)	4/20 (16% e4+)	30/67 (30% e4+)		0.209
Memory Measures				
MMSE	29(1)	29(1)	U = 890, z = -2.34	0.020
Logical Memory II	15(6)	13(4)	U = 5940, z = -2.62	0.009
Cognitive (z-scores)				
Executive Func.	0.26 (0.82)	-0.34 (1.17)	U = 1825, z = 3.89	0.000 **
Proc. Speed	-0.04 (0.70)	-0.24 (1.15)	U = 1592, z = 2.41	0.016 **

Notes: Mdn = median, IQR = interquartile range,

**
p < 0.01

*
p < 0.05; For Biomarker data only 96/100 Typical Performers had data available.

Table 2

Group Differences between Optimal Maintainers and Optimal Non-Maintainers at Baseline.

	Optimal Maintainer (n = 16) Mdn (IQR)	Optimal Non-Maintainer (n = 7) Mdn (IQR)	Significance Testing	p-value
Demographic				
Age (yrs)	77(6.38)	81(6.75)	U = 45, z = -0.74	0.492
Sex (M/F)	4/11	4/4		0.182
Education (yrs)	16(6)	18(8)	U = 47, z = -0.62	0.579
Verbal IQ	123(11)	129(5)	U = 37.5, z = -1.24	0.222
Biomarkers				
Amyloid-PET (DVR)	1.11(0.16)	1.43(0.26)	U = 13, z = -2.58	0.008 *
Hipp. Vol. (mm ³)	7530(896)	6966(431)	U = 70, z = 0.35	0.376
ApoE-4 (+/-)	2/13 (13% e4+)	2/5 (29% e4+)		0.565
Memory Measures				
MMSE	29(1)	29(2)	U = 46, z = -0.718	0.535
Logical Memory II	15(6)	14(9)	U = 49.5, z = -0.436	0.671
Cognitive (z-scores)				
Executive Func.	0.28(0.76)	0.42(1.95)	U = 45, z = -0.74	0.492
Proc. Speed	-0.06(0.62)	-0.03(2.09)	U = 23, z = -0.20	0.871

Notes: Mdn = median, IQR = interquartile range,

*
p < 0.05**
p < 0.01; For Biomarker data only 14/16 Maintainers and only 5/7 Non-Maintainers had data available.