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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.
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 and16 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.

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

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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 and 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 and 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 et al., 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 and 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 s (Benton et al., 1983) production of animals, fruits and vegetables in 60 s (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 3 T 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 = 2300/2.95/900 ms, flip angle = 9°, 1.1 × 1.1 × 1.2 mm 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-min 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.

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