Title

Cognitive aging is not created equally: differentiating unique cognitive phenotypes in “normal” adults

Authors

Casaletto, Kaitlin B
Elahi, Fanny M
Staffaroni, Adam M
et al.

Publication Date

2019-05-01

DOI

10.1016/j.neurobiolaging.2019.01.007

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Neurobiol Aging. 2019 May ; 77: 13–19. doi:10.1016/j.neurobiolaging.2019.01.007.

Cognitive Aging is Not Created Equally: Differentiating Unique Cognitive Phenotypes in "Normal" Adults

Kaitlin B. Casaletto, Ph.D., **Fanny M. Elahi, M.D., Ph.D.**, **Adam M. Staffaroni, Ph.D.**, **Samantha Walters, B.S.**, **Wilfredo Rivera Contreras, B.S.**, **Amy Wolf, B.S.**, **Dena Dubal, M.D., Ph.D.**, **Bruce Miller, M.D.**, **Kristine Yaffe, M.D.**, and **Joel H. Kramer, Psy.D.**

Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA

Abstract

Age-related cognitive decline is a public health problem, but highly diverse and difficult to predict. We captured non-overlapping cognitive phenotypes in high-functioning adults and identified baseline factors differentiating trajectories. 314 functionally normal adults (*M*=69y) completed 2+ visits. Participants with sample-based longitudinal slopes in memory or processing speed <−1SD were classified as "declining" on that measure. 29 and 50 individuals fell <−1SD on processing speed or memory slopes, respectively; 2.5% met criteria for both, who were excluded. At baseline, speed decliners demonstrated greater age, inflammation, and cognitive complaints compared to speed stable adults; memory decliners were more likely to be male, and had lower depressive symptoms, gray matter volumes, and white matter hyperintensities (WMH) compared to memory stable adults. Baseline speed, TNFα, and cognitive complaints accurately classified 96.3% of future speed decliners; baseline memory, sex, precuneal volume, and WMH accurately classified 88.5% of future memory decliners. There are discrete cognitive aging phenotypes reflecting *non-overlapping* vulnerabilities in high-functioning adults. Early markers can predict cognition even within the "normal" spectrum and underscore therapeutic targets.

Keywords

Episodic memory; processing speed; cytokines; neuroimaging; mood; Alzheimer's disease

1.1 Introduction

Cognitive aging is a highly heterogeneous clinical phenomenon with equally diverse underlying biology. The Einstein Aging study recently identified that up to *nine* unique "cognitive classes" best fit their data in a large cross-sectional cohort of non-demented older adults using a data-driven approach (latent class modeling)(Zammit et al., 2018). Similarly,

Corresponding author: Kaitlin B. Casaletto, Ph.D., Assistant Professor, Memory and Aging Center, Department of Neurology, UCSF, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, Kaitlin.casaletto@ucsf.edu, (p) (415) 476-1883, (f) (415) 476-5573.

in typically aging adults followed for 7-years in the Geneva Variability Study, Mella and colleagues (2018) demonstrated that although an overall group-level decline was measurable, particularly in processing speed and executive functions, high intra-individual variability was the norm (Mella et al., 2018). In fact, 35–50% of the sample showed stability or improvement across a comprehensive battery for the near-decade study period. Although "cognitive aging" is commonly discussed as a singular omnibus entity, the concept of idiosyncratic cognitive aging trajectories is much more consistent with the highly diverse biology of the aging brain. Models of neurologic aging include a host of upstream and downstream pathways, including immune dysregulation and changes in blood-brain permeability, oxidative stress and mitochondrial dysfunction, and aberrant protein misfolding and accumulation (e.g., $A\beta_{1-42}$, TDP43)(Erikson et al., 2016; Franceschi et al., 2000; López-Otín et al., 2013; Morrison and Baxter, 2012; Rahimi and Kovacs, 2014), that may each drive a specific clinical phenomenology – the unique combination(s) of which are even more diverse (Boyle et al., 2018). In fact, multimodal brain imaging approaches suggest a dynamic, multifactorial aging process during which there may be both sequential sets of events, as well as simultaneous processes occurring across the lifespan that may even differ by individual(Fjell et al., 2016). For example, hippocampal-based networks better predict memory functioning in younger adults, while fronto-striatal networks better memory functioning in older adults; additionally while brain structure demonstrates a largely monotonic trend, functional connectivity appears to be nonlinear across ages. These data suggest that potentially unique brain networks subserve the same cognitive skill differently across age epochs. Appreciation and quantification of this variability inherent even within "normative" cognitive aging is an important addition to the aging nomenclature to parse out and potentially support the temporal sequence these different mechanisms.

Deep characterization of diverse presentations of brain aging will not only inform our understanding of the spectrum and pathophysiological development of age-related neurodegenerative processes, but also point to early potential preventative targets to support the aging brain. Age is the greatest risk factor for developing a neurodegenerative syndrome and more than a third of otherwise clinically normal adults exhibit clinicopathologically significant levels of pathology at autopsy (Negash et al., 2011). These findings blur the line of what is considered "normal" versus "pathological" in aging and encourage a framework of neurologic aging on a spectrum of neurodegeneration. Given this, identification of specific neurologic aging trajectories may be highly useful to identify the earliest "pathological" processes that are commonly present even within clinically normal adults that could be predictive of a specific aging phenotype. By 2030, the number of adults >65 years-old is estimated to exceed that of children (Bureau, n.d.); there is a huge public health need to identify clinically relevant (and potentially modifiable) factors that are associated with sub-optimal aging. Even incremental preventative improvements in cognitive health will have massive downstream public health benefits (Barnes and Yaffe, 2011; Norton et al., 2014). Measurable markers that can differentiate risk for *specific* less-than-optimal cognitive aging paths will lead to the most potent targets for individually-tailored brain health programs.

We aimed to leverage a highly characterized longitudinal cohort of high-functioning adults to: 1) identify non-overlapping cognitive aging phenotypes, and 2) characterize *baseline*

clinical and biological factors that differentiate individuals who go on to develop each phenotype.

2.1. Methods

2.2. Participants.

314 participants who completed at least two annual study visits as part of the University of California, San Francisco Memory and Aging Center healthy aging study were included. Participants represent a community-dwelling, convenience sample of the Bay Area collected between 2000–2017, largely recruited via newspaper advertisements, flyers, and community outreach events. All participants underwent comprehensive neurological and neuropsychological evaluations, including study partner interview, and met the following criteria *at every study visit*: 1) no diagnosed memory or neurological condition (e.g., epilepsy, stroke), and 2) no functional decline as operationalized as a Clinical Dementia Rating scale of 0 (via study partner interviews). The California Verbal Learning Test was administered since the inception of this longitudinal study and all included study participants had available data at two or more time points (n=314 with 1249 observations; M=4.6 total years in study); however, administration of the processing speed measures began in 2008 and therefore a subset of individuals had two or more available time points on this measure (n=180 with 493 observations; M=3.9 total years in study)(see Table 1 for further participant characterization).

2.3 Neuropsychological Measures.

We selected episodic memory and processing speed as cognitive phenotypes of interest given their clinical relevance and to tap into relatively distinct cognitive domains to examine *non-overlapping* cognitive trajectories. *Episodic memory* was measured via the California Verbal Learning Test-second edition (CVLT-II), a widely validated and implemented measure of verbal episodic memory (Delis et al., 2000). Total long delay (20–30 minute) free recall raw scores were our primary memory variable of interest (range: 0–16). *Processing speed* was measured using a computerized battery of visual reaction-time based measures; measures were combined into a composite z-score. This battery has been previously described elsewhere (Casaletto et al., 2018) and validated as sensitive to neurologic aging (Kerchner et al., 2012).

2.4. Psychological Measures.

We measured depressive symptoms with the Geriatric Depression Scale (GDS), a self-reported screener of depressive symptoms developed for older adults, and everyday cognitive complaints via the Everyday Cognition Self-Report Scale (ECog)(Farias et al., 2008).

2.5. Laboratory markers of inflammation.

Baseline 12h fasting blood draws were analyzed for a panel of plasma-based cytokine markers of global immune activation – interleukin-6 (IL6) and tumor necrosis factor-alpha (TNFα) -- and chemokine markers more specific to monocyte/macrophage activation -- macrophage inflammatory protein 1-alpha (MIP1α; CCL3), macrophage inflammatory

protein 1-beta (MIP1β; CCL4), and macrophage derived chemokine (MDC). We chose IL6 and TNFα given their known involvement in multiple pro-inflammatory pathways, disrupted signaling in aging, and consistently reported relationship with age-related cognition (Bettcher and Kramer, 2014; Perry, 2010; Tanaka et al., 2014). We additionally chose to include markers of monocyte/macrophage inflammation given that this is a particularly important pathway in age-related immunosenescence (Franceschi et al., 2000; Gomez et al., 2005). All analyses were conducted via Meso Scale Diagnostics (Rockville, MD, USA) V-PLEX kits following standard manufacturer guidelines.

2.6. Neuroimaging.

Participants completed 3T magnetic resonance imaging within 180 days of their baseline visit (n=288). Participants who received neuroimaging did not differ on age, education, baseline MMSE, memory or processing speed performances compared to those who did not. Notably, there were more males who completed neuroimaging (p=0.005), which we adjusted for in all imaging-related models.

Acquisition Parameters.—Participants completed a 3T Magnetom Vision TIM Siemens Trio system (Siemens, Iselin, NJ) magnetic resonance imaging (MRI) scan within 180 days of their neuropsychological evaluation. A T1-weighted MP-RAGE structural scan was acquired with an acquisition time=8 min 53 sec, sagittal orientation, a field of view of 160 × 240 × 256 mm with an isotropic voxel resolution of 1 mm^3, TR=2300 ms, TE=2.98 ms, TI=900 ms, flip angle=9°.

T1 Processing.—Before processing, all T1-weighted images were visually inspected for quality. Images with excessive motion or image artifact were excluded. Magnetic field bias was corrected using the N3 algorithm(Sled et al., 1998). Tissue segmentation was performed using the unified segmentation procedure in SPM12(Ashburner and Friston, 2005). Each participant's T1-weighted image was warped to create a study-specific template using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007); subsequently, the images were normalized and modulated in the study-specific template space using non-linear and rigid-body registration. Images were smoothed using a 8mm Gaussian kernel with 8-mm full width half maximum. For registration with a brain parcellation atlas, linear and non-linear transformations between DARTEL's space and ICBM space were applied(Mazziotta et al., 1995). Quantification of volumes in specific brain regions at each time point was accomplished by transforming a standard parcellation atlas into ICBM space and summing all modulated gray matter within each parcellated region(Desikan et al., 2006). Total Intracranial Volume (TIV) was estimated for each subject in MNI space.

Gray Matter Regions of Interest.—Gray matter regions of interest (ROIs) were selected *a priori* based on regions of known vulnerability in aging and Alzheimer's-related processes. ROIs from the Desikan atlas were summed to examine the following bilateral regions: 1) dorsolateral prefrontal cortex (caudal and rostral middle frontal gyrus), 2) parietal lobes, 3) precuneus, 4) amygdala, 5) hippocampus, and 6) subcortical volumes (thalamus, putamen, and caudate).

White Matter Hyperintensity Volumes.—White matter hyperintensities (WMH) were segmented using FLAIR and T1-weighted images (n=193). We visually inspected the raw scans for quality control. The WMH segmentation process is fully automated, is based on a regression algorithm, and uses a Hidden Markov Random Field with Expectation Maximization software(Avants et al., 2011; Dadar et al., 2017).

2.7. Statistical Analyses

Classification of Cognitive Phenotypes.—To classify individuals into longitudinal cognitive phenotypes, we conducted linear mixed-effects regressions allowing for random intercepts and slopes modeling the effect of years in study (time) on processing speed and episodic memory, separately. Based on these model parameters, individual-specific slopes for processing speed and memory were fitted for each participant. We then classified individuals with slopes falling in the bottom 16^{th} percentile (corresponding with 1 SD on a normal curve) of the sample as "decliners" while those with slopes in the upper 84^{th} percentile were classified as "stable" on the given measure (Heaton et al., 2004). It is important to note that although we derived a −1SD "declining" cut-point within our sample, these data represent an independently--functioning cohort of clinically normal older adults overall – i.e., these individuals are simply at the outlying ends of the normal curve (not "impaired"). We elected to classify individuals into groups (versus continuous modeling) to determine if it was possible to identify and differentiate specific "at-risk" subgroups. Particularly within a cohort of typically aging adults, the ability to detect potential differentiating factors sensitive to future decline is highly desirable (i.e., identify individual who may be at-risk for future decline who are currently in the asymptomatic stages). To this end, we selected a cut-off approach to allow for calculation of more clinically meaningful predictive parameters (e.g., classification rates).

Baseline Predictors.—Once the phenotypes were defined, we conducted ANCOVA models to examine the baseline (cross-sectional) group differences (declining vs. stable) on our variables of interest (demographics, psychological measures, plasma cytokines, and neuroimaging), separately for the memory and speed phenotypes. Finally, to determine the best set of baseline predictors, we entered those variables that significantly ($p<0.05$) differentiated between the declining vs. stable phenotypes into a forward, combined direction stepwise logistic regression model with a minimum AICc stopping rule.

3.1. Results

Overall, our sample demonstrated improving memory (b=0.04, p=0.06) and very subtle speed declines (b=−0.04, p=0.001) over time. In other words, as a group, our cohort improved at a rate of 0.04 words recalled on the CVLT per year, and declined 0.04 z-score points on the processing speed composite per year. At baseline, 29 adults (16.1%) met criteria for a declining speed slope across time (decliners b=−0.10, p=0.07; "processing speed phenotype"), while 151 demonstrated stable processing speed. On memory testing, at baseline, 50 individuals (15.9%) met criteria for a declining memory slope (decliners b=−0.42, p<0.001; "memory phenotype"), while 264 showed stable memory performances across time. Notably, these data-derived cohorts were largely orthogonal; at baseline, only

n=7 (2.5%) individuals met criteria for both declining speed and memory phenotypes. We excluded these 7 individuals from subsequent analyses to more clearly determine the biological and clinical predictors of *unique* cognitive trajectories.

3.1.2. Processing Speed Phenotype.

At baseline, adults who developed the slowed processing speed phenotype demonstrated slower baseline processing speed performances (t(171)= −12.2, p<0.001) compared to speed stable adults. After adjusting for baseline processing speed, older age at baseline significantly differentiated between speed declining versus stable individuals (b=2.6, p=0.003). There were no significant group differences on sex (χ^2=0.10, p=0.75) or education (t(171)=1.4, p=0.15).

Adjusting for age, sex, education, and baseline processing speed, at baseline, adults who developed a declining speed phenotype demonstrated higher concentrations of IL6 (b=0.29, p=0.003), TNFα (b=0.10, p=0.047), MIP1α (b=0.14, p=0.03), and MDC (b=0.12, 0.02), as well as endorsed more cognitive symptoms at baseline (ECog; b=0.05, p=0.04) compared to speed stable adults. The speed phenotypes did not differ on baseline MIP1β concentrations (b=0.06, p=0.30) or depressive symptoms (b=0.45, p=0.32). Notably, at baseline, adults with a declining processing speed phenotype also did not significantly differ from speed stable adults on cortical grey matter ROIs (ps>0.30), white matter hyperintensity volumes (b=0.05, p=0.82), or *APOEε4* (χ^2=0.17, p=0.68)(Figure 1).

We then entered age, baseline processing speed, IL-6, MIP1a, MDC, TNFα, and ECog scores as possible regressors into our final stepwise model. The best fitting model (BIC=26.6, AICc=17.5, $X^2(3)$=74.74, p<0.001) included baseline processing speed, TNFα, and perceived cognitive symptoms (see Table 2). These three baseline factors explained 89.3% (entropy R^2) of the variance with a 96.3% accurate classification rate differentiating between those who went on to develop a declining versus stable processing speed phenotype.

3.1.3. Episodic Memory Phenotype.

At baseline, individuals who went on to evidence a declining memory phenotype demonstrated better memory performances at their first visit compared to those with stable memory performances (t(304)=−2.3, p=0.02). After adjusting for baseline memory performances, men were at a higher risk of developing a memory phenotype than women (OR=1.9, 95%CI=1.05, 3.62; χ^2=4.5, p=0.03); the memory phenotypes did not differ on age (t(304)=−0.35, p=0.73) or education (t(304)=0.59, p=0.55).

Adjusting for age, sex, education, baseline memory, and total intracranial volumes, at baseline, adults with a declining memory phenotype demonstrated smaller bilateral parietal (b= −1.37, p=0.046), precuneus (b= −0.41, p=0.038), and amygdala (b= −0.03, p=0.03) gray matter volumes, as well as *less* white matter hyperintensity burden (b= −0.25, p=0.049) compared to memory stable adults. Smaller subcortical (b=−0.24, p=0.09) and hippocampal (b=−0.06, p=0.085) volumes approached but did not reach statistical significance, while dorsolateral prefrontal volumes did not differ between groups (b=−0.03, p=0.88). Individuals with a declining memory phenotype also demonstrated significantly *fewer* depressive

symptoms at baseline compared to those with stable memory phenotypes (GDS b=−0.54, p=0.03), but did not differ on cognitive complaints (ECog b=−0.01, p=0.66). The memory phenotypes also did not significantly differ on any plasma cytokine markers (b range= −0.06–0.02; ps>0.55), or *APOEε4* (b=−0.02, p=0.93)(Figure 1).

We entered baseline memory, sex, parietal, precuneus, amygdala, and white matter hyperintensity volumes, and GDS as possible regressors into our final stepwise model. The best model (BIC=85.0, AICc=73.3, $X^2(4)=24.7$, p<0.001) included baseline memory, sex, precuneus and white matter hyperintensity volumes (Table 2). These baseline regressors accounted for 28.3% (entropy R^2) of the variance with an 86.6% accurate classification rate identifying individuals at baseline who went on to develop a memory declining versus stable phenotype.

4.1. Discussion

In a cohort of comprehensively evaluated, high-functioning older adults, we found evidence for distinct cognitive aging trajectories with *non-overlapping* biological and clinical characteristics at baseline. Though the groups were data-derived, discrete processing speed or episodic memory phenotypes were identified such that <3% of the sample met criteria for both. Most interestingly, there was a clear pattern of baseline characteristics that distinguished individuals who went on to develop a speed or memory declining phenotype. Older age, endorsement of psychological distress, and immune activation differentiated between speed declining versus stable phenotypes; whereas male sex, less psychological distress, smaller gray matter volumes, and less white matter injury were associated with an increased likelihood of exhibiting a memory declining phenotype. Final multivariable models suggested high classification accuracy (>88%) was possible when including the best combination of baseline traits to predict subsequent cognitive aging phenotypes. Most notably, these groups were detectable and predictable, even within an otherwise clinically normal cohort of adults with particularly mild levels of decline (memory: −0.4 words/year; processing speed: −0.1 z-score points/year). The high accuracy with which we were able to predict subsequent phenotypes even within the normal spectrum also underscores the important potential of these early markers as possible risk stratification tools and/or therapeutic targets for dementia prevention.

Though tempting to consider these declining phenotypes as “preclinical”, it is important to keep in mind that these individuals were otherwise functioning independently in the community, indistinguishable from their “stable” peers at their annual study evaluation, and that our cut-points (and nomenclature of “declining”) were artificially imposed on the data. Although demarcation of such groups is a useful research tool to better understand these processes, including classification metrics for at-risk groups and future operationalization of clinically meaningful parameters, neurologic aging is likely a more continuous phenomenon. Importantly, our data suggest that detectable clinical changes (e.g., cognitive performances) appear to reflect a measurable pathological correlate, even among individuals within the “normative” spectrum. Of course, it is important to appreciate that some pathologies are simply more common in aging and many are reversible in nature (not progressive or degenerative like AD). However, particularly in the clinical context of typical aging, we

argue that measureable clinical decline is a real phenomenon with a pathological (though not necessarily progressive) CNS correlate. Our ability to detect and predict these declining phenotypes within the normative spectrum sheds light into the dynamic nature of cognitive aging and, given their unique characteristics, provides insight into points for at-risk monitoring and primary prevention to support healthful brain aging.

Delving more deeply into those who developed a slower processing speed trajectory, we observed an age, psychological, and immune phenotype at baseline. It is difficult to determine which of these processes are more upstream (causative) versus downstream of each other, though it is notable that they were each related to further processing speed declines at follow-up. Slowed processing is one of the most common symptoms of neurologic aging, and some groups argue that it is *the* hallmark of aging underlying all other cognitive changes (Salthouse, 1996, 2000); this is consistent with our finding that individuals who showed the steepest speed declines were in fact the oldest. The mechanism(s) driving this effect are less clear. One possibility may be related to the immune system. We found markers of both higher global and monocyte/macrophage inflammation in the processing speed decliners. Loss of function of the immune system is a consistently reported phenomenon in aging. Though a highly pleiotropic and bidirectional process, in aging, the cumulative effects of loss of immune naivety, prolonged instigation of active/reactive microglia and astrocytes, and ensuing states of chronic inflammation are collectively coined “immunosenescence” (Franceschi et al., 2000; Gomez et al., 2005). Such dysregulation of the immune system has been linked to slowed processing speed both in aging and primary autoimmune conditions (Eckert, 2011; Heringa et al., 2014; Hughes et al., 2011; Shucard et al., 2007), and our finding that it may be both detectable and *predictive* of faster declines in processing speed supports a potential upstream role of the immune system in cognitive aging. Commensurate with these findings, a recent study demonstrated that higher concentrations of a systemic inflammatory marker (C-reactive protein) in middle-to-late age was significantly associated with cerebral white matter injury 14-years later (Walker et al., 2018). These converging findings support the predictive validity of peripherally-based cytokine markers and the immune system as an important target to promote future brain health states. Individuals who went on to develop a processing speed declining phenotype additionally endorsed more cognitive complaints at baseline, which is in direct contrast to the memory declining phenotype who demonstrated *less* baseline psychological distress (fewer depressive symptoms). The processing speed declining individuals appear to represent a distinct group who may be demonstrating a heightened psychological state, perhaps reflecting awareness of these incipient cognitive changes and/or reflecting a common vulnerable pathway. Regarding the latter, frontostriatal network dysfunction commonly results in both processing speed impairment and are affected in psychiatric disease (Marsh et al., 2009; Turken et al., 2008; Walsh et al., 2017). This same pattern of both elevated inflammatory and psychological activation in the processing speed group is commensurate with these studies and raises the question of the role of the immune system as a mediator of individuals’ psychological experiences. Indeed, recent works are underscoring the important role of immune functioning in psychiatric health; for example, Kiraly and colleagues (Kiraly et al., 2017) demonstrated heightened peripheral inflammation in adults with treatment refractory depression and Hellmuth et al. (Hellmuth et al., 2017) showed that

markers of cytokine activation were associated with mood symptomology in acute HIV infection (immune deprived state). Taken together, these data support that processing speed, immune activation, and psychological symptoms may represent a constellation of factors that interplay to result in one possible unique neurologic aging phenotype.

In contrast, individuals who went on to develop a declining episodic memory trajectory tended to be male and demonstrated a cortical vulnerability phenomenology. Converging lines of research support sex differences in brain aging (Dubal and Rogine, 2017; Nebel et al., 2018). For instance, typically aging men consistently demonstrate steeper declines in both brain volume and cognition compared to women over time, and episodic memory is specifically the most consistently reported domain to demonstrate sex effects with men performing more poorly than females across ages (Casaletto et al., 2015; Herlitz and Rehnman, 2008; Josefsson et al., 2012; Kramer et al., 1997). Indeed, our findings are remarkably consistent with a recent cross-sectional study conducted in a large cohort of young-to-older adults demonstrating that males had significantly more severe memory and hippocampal volume declines across ages compared to females (Jack et al., 2015). Though the pathways are not fully delineated, sex chromosomes appear to play an important and possibly mechanistic role in animal models. Dubal and colleagues (2012) demonstrated that in amyloid precursor protein transgenic mice engineered to have either male (testes) or female (ovaries) sex organs (regardless of sex chromosome), genetically male mice died faster than female mice regardless of their sex organs. Identification of sex-related resilience and/or risk pathways that may be driving these differences is an exciting area of future work with high potential to reveal novel aspects of the aging process (Dubal et al., 2012). Additionally, independent of sex, our finding that individuals who developed steeper memory declines had smaller gray matter volumes in both dorsal-posterior cortical and subcortical regions and less white matter injury raises the question of if we are illustrating risk of premorbid developmental differences and/or capturing an atrophying network in a vulnerable system. Previous works support this concept that reductions in cortical thickness are a steady, measurable phenomenon in adulthood across all regions that appears to be genetically-linked to changes in developmental regions; in other words, the developmental trajectories of early regions appear to predict future regions of vulnerability in aging(Fjell et al., 2015). Interestingly, while some studies of typical aging indicate that cortical temporal regions are particularly vulnerable in amyloid positive individuals (indicative of an emerging AD processes)(Oh et al., 2014), other studies suggest that fronto-temporal atrophy is present even in adults with low probability of AD(Fjell et al., 2013). We are not able to disentangle the possible contribution of prodromal AD processes, but rather continue to support the well-established concept that episodic memory is tightly linked with and particularly sensitive to cortical integrity more broadly (Fletcher et al., 2018; Leong et al., 2017).

Our study has several limitations. These data represent a largely homogeneous convenience sample of White, well-educated, Bay Area adults who may not be reflective of the larger aging population. Though some of our results are consistent with findings thus far in more diverse samples (e.g.,.(Fletcher et al., 2018);(Leong et al., 2017)), more work is clearly needed to support the generalizability of these findings in cohorts who may potentially carry other brain health risk factors (e.g., genetic and metabolic differences, etc.). There were also more males in the subset of individuals who received neuroimaging, which may limit the

generalizability of the imaging models. However, we adjusted to sex in all imaging models regardless to help mitigate this limitation. Interestingly, although it did not reach statistical significance, episodic memory performances *increased* as a whole group in our cohort of typically aging adults. Although this could represent psychometric noise and unwanted "practice effects", there is growing evidence that episodic memory decline with age may not be a "typical" aging phenomenon. For instance, in a recent study, Harrington et al. (2018) (Harrington et al., 2018) selected a cohort of older adults who were clinically normal at baseline and followed them longitudinally. Initially, in this study, there was a significant, negative association between age and memory; however, once the authors removed all participants who subsequently developed MCI or were AB+ PET, there was no longer an association between age and memory. Together, these data may suggest that declines in memory performances over time may not be an "expected" phenomenon. It is also important to note that our participants who eventually went on to decline in memory performances demonstrated better performances initially than those who remained stable. Though this finding could indicate regression to the mean, this seemed less likely given the consistent pattern of baseline risk factors that significantly differentiated these individuals (e.g., smaller cortical volumes). Future work is clearly needed to replicate our models, including deeply characterizing the identified cohorts and risk factors.

Our data support that "typical" cognitive aging includes discrete and diverse phenotypes reflecting equally disparate underlying vulnerabilities. We argue that the spectrum of neurologic aging to degeneration are overlapping and appreciation of this broadened framework may encourage new ways of thinking about how we approach age-related brain diseases, including identification of resilience and risk factors, and intervention points to promote brain health for our aging population.

Acknowledgements

This study was supported by NIH-NIA grants K23AG058752 (PI: Casaletto), L30AG057123 (PI: Casaletto), 1R01AG032289 (PI: Kramer), R01AG048234 (PI: Kramer), and UCSF ADRC P50 AG023501. Our work was also supported by Larry L. Hillblom Network Grant (PI: Kramer; 2014-A-004-NET) and Fellowship Grant (PI: Casaletto; 2017-A-004-FEL).

References

Ashburner J, 2007 A fast diffeomorphic image registration algorithm. Neuroimage. 10.1016/j.neuroimage.2007.07.007

Ashburner J, Friston KJ, 2005 Unified segmentation. Neuroimage. 10.1016/j.neuroimage.2005.02.018

Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC, 2011 An open source multivariate framework for N-tissue segmentation with evaluation on public data. Neuroinformatics 10.1007/s12021-011-9109-y

Barnes DE, Yaffe K, 2011 The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet. Neurol 10, 819–28. 10.1016/S1474-4422(11)70072-2 [PubMed: 21775213]

Bettcher B, Kramer J, 2014 Longitudinal Inflammation, Cognitive Decline, and Alzheimer's Disease: A Mini-Review. 10.1038/clpt.2014.147

Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA, 2018 Person-specific contribution of neuropathologies to cognitive loss in old age. Ann. Neurol 83, 74–83. 10.1002/ana.25123 [PubMed: 29244218]

Bureau UC, n.d. Older People Projected to Outnumber Children.

Casaletto KB, Staffaroni AM, Elahi F, Fox E, Crittenden PA, You M, Neuhaus J, Glymour M, Bettcher BM, Yaffe K, Kramer JH, 2018 Perceived Stress is Associated with Accelerated Monocyte/Macrophage Aging Trajectories in Clinically Normal Adults. Am. J. Geriatr. Psychiatry 10.1016/j.jagp.2018.05.004

Casaletto KB, Umlauf A, Beaumont J, Gershon R, Slotkin J, Akshoomoff N, Heaton RK, 2015 Demographically Corrected Normative Standards for the English Version of the NIH Toolbox Cognition Battery. J. Int. Neuropsychol. Soc 21 10.1017/S1355617715000351

Dadar M, Pascoal TA, Manitsirikul S, Misquitta K, Fonov VS, Tartaglia MC, Breitner J, Rosa-Neto P, Carmichael OT, Decarli C, Collins DL, 2017 Validation of a Regression Technique for Segmentation of White Matter Hyperintensities in Alzheimer's Disease. IEEE Trans. Med. Imaging 10.1109/TMI.2017.2693978

Delis DC, Kramer JH, Kaplan E, Ober BA, 2000 California Verbal Learning Test – second edition. Adult version. Manual. Test

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ, 2006 An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 10.1016/j.neuroimage.2006.01.021

Dubal DB, Broestl L, Worden K, 2012 Sex and gonadal hormones in mouse models of Alzheimer's disease: what is relevant to the human condition? Biol. Sex Differ 3, 24 10.1186/2042-6410-3-24 [PubMed: 23126652]

Dubal DB, Rogine C, 2017 Apolipoprotein E ε4 and Risk Factors for Alzheimer Disease—Let's Talk About Sex. JAMA Neurol. 74, 1167 10.1001/jamaneurol.2017.1470 [PubMed: 28846761]

Eckert MA, 2011 Slowing Down: Age-Related Neurobiological Predictors of Processing Speed. Front. Neurosci 5, 25 10.3389/fnins.2011.00025 [PubMed: 21441995]

Erikson GA, Bodian DL, Rueda M, Molparia B, Scott ER, Scott-Van Zeeland AA, Topol SE, Wineinger NE, Niederhuber JE, Topol EJ, Torkamani A, 2016 Whole-Genome Sequencing of a Healthy Aging Cohort. Cell 10.1016/j.cell.2016.03.022

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, Decarli C, 2008 The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology 22, 531–44. 10.1037/0894-4105.22.4.531 [PubMed: 18590364]

Fjell AM, Grydeland H, Krogsrud SK, Amlien I, Rohani DA, Ferschmann L, Storsve AB, Tamnes CK, Sala-Llonch R, Due-Tønnessen P, Bjørnerud A, Sølsnes AE, Håberg AK, Skranes J, Bartsch H, Chen C-H, Thompson WK, Panizzon MS, Kremen WS, Dale AM, Walhovd KB, 2015 Development and aging of cortical thickness correspond to genetic organization patterns. Proc. Natl. Acad. Sci 10.1073/pnas.1508831112

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB, 2013 Brain Changes in Older Adults at Very Low Risk for Alzheimer's Disease. J. Neurosci 10.1523/JNEUROSCI.5506-12.2013

Fjell AM, Sneve MH, Storsve AB, Grydeland H, Yendiki A, Walhovd KB, 2016 Brain Events Underlying Episodic Memory Changes in Aging: A Longitudinal Investigation of Structural and Functional Connectivity. Cereb. Cortex 10.1093/cercor/bhv102

Fletcher E, Gavett B, Harvey D, Farias ST, Olichney J, Beckett L, DeCarli C, Mungas D, 2018 Brain volume change and cognitive trajectories in aging. Neuropsychology 32, 436–449. 10.1037/neu0000447 [PubMed: 29494196]

Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G, 2000 Inflamm-aging: An Evolutionary Perspective on Immunosenescence. Annals 908, 244–254.

Gomez CR, Boehmer ED, Kovacs EJ, 2005 The aging innate immune system. Curr. Opin. Immunol 17, 457–462. 10.1016/j.coi.2005.07.013 [PubMed: 16084711]

Harrington KD, Schembri A, Lim YY, Dang C, Ames D, Hassenstab J, Laws SM, Rainey-Smith S, Robertson J, Rowe CC, Sohrabi HR, Salvado O, Weinborn M, Villemagne VL, Masters CL, Maruff P, 2018 Estimates of age-related memory decline are inflated by unrecognized Alzheimer's disease. Neurobiol. Aging 10.1016/j.neurobiolaging.2018.06.005

Heaton RK, Miller W, Taylor MJ, Grant I, 2004 Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Psychological Assessment Resources.

Hellmuth J, Colby D, Valcour V, Suttichom D, Spudich S, Ananworanich J, Prueksakaew P, Sailasuta N, Allen I, Jagodzinski LL, Slike B, Ochi D, Paul R, Group, on behalf of the R. 010 S., 2017 Depression and Anxiety are Common in Acute HIV Infection and Associate with Plasma Immune Activation. AIDS Behav. 21, 3238–3246. 10.1007/s10461-017-1788-4 [PubMed: 28484888]

Heringa SM, van den Berg E, Reijmer YD, Nijpels G, Stehouwer CDA, Schalkwijk CG, Teerlink T, Scheffer PG, van den Hurk K, Kappelle LJ, Dekker JM, Biessels GJ, 2014 Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. Psychoneuroendocrinology 40, 108–18. 10.1016/j.psyneuen.2013.11.011 [PubMed: 24485482]

Herlitz A, Rehnman J, 2008 Sex Differences in Episodic Memory. Curr. Dir. Psychol. Sci 17, 52–56. 10.1111/j.1467-8721.2008.00547.x

Hughes AJ, Denney DR, Lynch SG, 2011 Reaction Time and Rapid Serial Processing Measures of Information Processing Speed in Multiple Sclerosis: Complexity, Compounding, and Augmentation. J. Int. Neuropsychol. Soc 17, 1113–1121. 10.1017/S1355617711001135 [PubMed: 22040901]

Jack CR, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda MM, Gregg BE, Pankratz VS, Rocca WA, Petersen RC, 2015 Age, Sex, and *APOE* ε4 Effects on Memory, Brain Structure, and β-Amyloid Across the Adult Life Span. JAMA Neurol. 72, 511 10.1001/jamaneurol.2014.4821 [PubMed: 25775353]

Josefsson M, de Luna X, Pudas S, Nilsson L-G, Nyberg L, 2012 Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. J. Am. Geriatr. Soc 10.1111/jgs.12000

Kerchner GA, Racine CA, Hale S, Wilheim R, Laluz V, Miller BL, Kramer JH, 2012 Cognitive Processing Speed in Older Adults: Relationship with White Matter Integrity. PLoS One 7 10.1371/journal.pone.0050425

Kiraly DD, Horn SR, Van Dam NT, Costi S, Schwartz J, Kim-Schulze S, Patel M, Hodes GE, Russo SJ, Merad M, Iosifescu DV, Charney DS, Murrough JW, 2017 Altered peripheral immune profiles in treatment-resistant depression: response to ketamine and prediction of treatment outcome. Transl. Psychiatry 7, e1065 10.1038/tp.2017.31 [PubMed: 28323284]

Kramer JH, Kaplan E, Delis DC, O'Donnell L, Prifitera A, 1997 Developmental sex differences in verbal learning. Neuropsychology 10.1037/0894-4105.11.4.577

Leong RLF, Lo JC, Sim SKY, Zheng H, Tandi J, Zhou J, Chee MWL, 2017 Longitudinal brain structure and cognitive changes over 8 years in an East Asian cohort. Neuroimage 147, 852–860. 10.1016/J.NEUROIMAGE.2016.10.016 [PubMed: 27742600]

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G, 2013 XThe hallmarks of aging. Cell 10.1016/j.cell.2013.05.039

Marsh R, Maia TV, Peterson BS, 2009 Functional Disturbances Within Frontostriatal Circuits Across Multiple Childhood Psychopathologies. Am. J. Psychiatry 166, 664–674. 10.1176/appi.ajp.2009.08091354 [PubMed: 19448188]

Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J, 1995 A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage 2, 89–101. [PubMed: 9343592]

Mella N, Fagot D, Renaud O, Kliegel M, de Ribaupierre A, 2018 Individual Differences in Developmental Change: Quantifying the Amplitude and Heterogeneity in Cognitive Change across Old Age. J. Intell 6, 10 10.3390/jintelligence6010010

Morrison JH, Baxter MG, 2012 The ageing cortical synapse: hallmarks and implications for cognitive decline. 10.1038/nrn3200

Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM, 2018 Understanding the impact of sex and gender in Alzheimer's disease: A call to action. Alzheimer's Dement 10.1016/j.jalz.2018.04.008

Negash S, Bennett DA, Wilson RS, Schneider JA, Arnold SE, 2011 Cognition and neuropathology in aging: multidimensional perspectives from the Rush Religious Orders Study and Rush Memory And Aging Project. Curr. Alzheimer Res 8, 336–40. [PubMed: 21222592]

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C, 2014 Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 10.1016/S1474-4422(14)70136-X

Oh H, Madison C, Villeneuve S, Markley C, Jagust WJ, 2014 Association of gray matter atrophy with age, β-amyloid, and cognition in aging. Cereb. Cortex 10.1093/cercor/bht017

Perry VH, 2010 Contribution of systemic inflammation to chronic neurodegeneration. Acta Neuropathol 10.1007/s00401-010-0722-x

Rahimi J, Kovacs GG, 2014 Prevalence of mixed pathologies in the aging brain. Alzheimer's Res. Ther 10.1186/s13195-014-0082-1

Salthouse T, 1996 The processing-speed theory of adult age differences in cognition. Psychol. Rev 103, 403–428. [PubMed: 8759042]

Salthouse TA, 2000 Aging and measures of processing speed. Biol. Psychol 54, 35–54. 10.1016/S0301-0511(00)00052-1 [PubMed: 11035219]

Shucard JL, Gaines JJ, Ambrus J, Shucard DW, 2007 C-reactive Protein and Cognitive Deficits in Systemic Lupus Erythematosus. Cogn. Behav. Neurol 20, 31–37. 10.1097/WNN.0b013e31802e3b9a [PubMed: 17356342]

Sled JG, Zijdenbos a P., Evans a C., 1998 A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans. Med. Imaging 10.1109/42.668698

Tanaka T, Narazaki M, Kishimoto T, 2014 IL-6 in inflammation, immunity, and disease. Cold Spring Harb. Perspect. Biol 6, a016295 10.1101/cshperspect.a016295 [PubMed: 25190079]

Turken U, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JDE, 2008 Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. Neuroimage 42, 1032–1044. 10.1016/J.NEUROIMAGE.2008.03.057 [PubMed: 18602840]

Walker KA, Windham BG, Power MC, Hoogeveen RC, Folsom AR, Ballantyne CM, Knopman DS, Selvin E, Jack CR, Gottesman RF, 2018 The association of mid-to late-life systemic inflammation with white matter structure in older adults: The Atherosclerosis Risk in Communities Study. Neurobiol. Aging 68, 26–33. 10.1016/J.NEUROBIOLAGING.2018.03.031 [PubMed: 29702373]

Walsh E, Carl H, Eisenlohr-Moul T, Minkel J, Crowther A, Moore T, Gibbs D, Petty C, Bizzell J, Smoski MJ, Dichter GS, 2017 Attenuation of Frontostriatal Connectivity During Reward Processing Predicts Response to Psychotherapy in Major Depressive Disorder. Neuropsychopharmacology 42, 831–843. 10.1038/npp.2016.179 [PubMed: 27585739]

Zammit AR, Hall CB, Lipton RB, Katz MJ, Muniz-Terrera G, 2018 Identification of Heterogeneous Cognitive Subgroups in Community-Dwelling Older Adults: A Latent Class Analysis of the Einstein Aging Study. J. Int. Neuropsychol. Soc 24, 511–523. 10.1017/S135561771700128X [PubMed: 29317003]

Highlights

- Are there unique, predictable cognitive trajectories in typical aging?
- We identified a declining memory or processing speed phenotype with <3% overlap
- Unique baseline predictors differentiated speed or memory decliners with >88% accuracy
- “Normal” cognitive aging is not a singular entity and may be a misnomer
- Early markers can predict “normal” aging phenotypes and highlight therapy targets

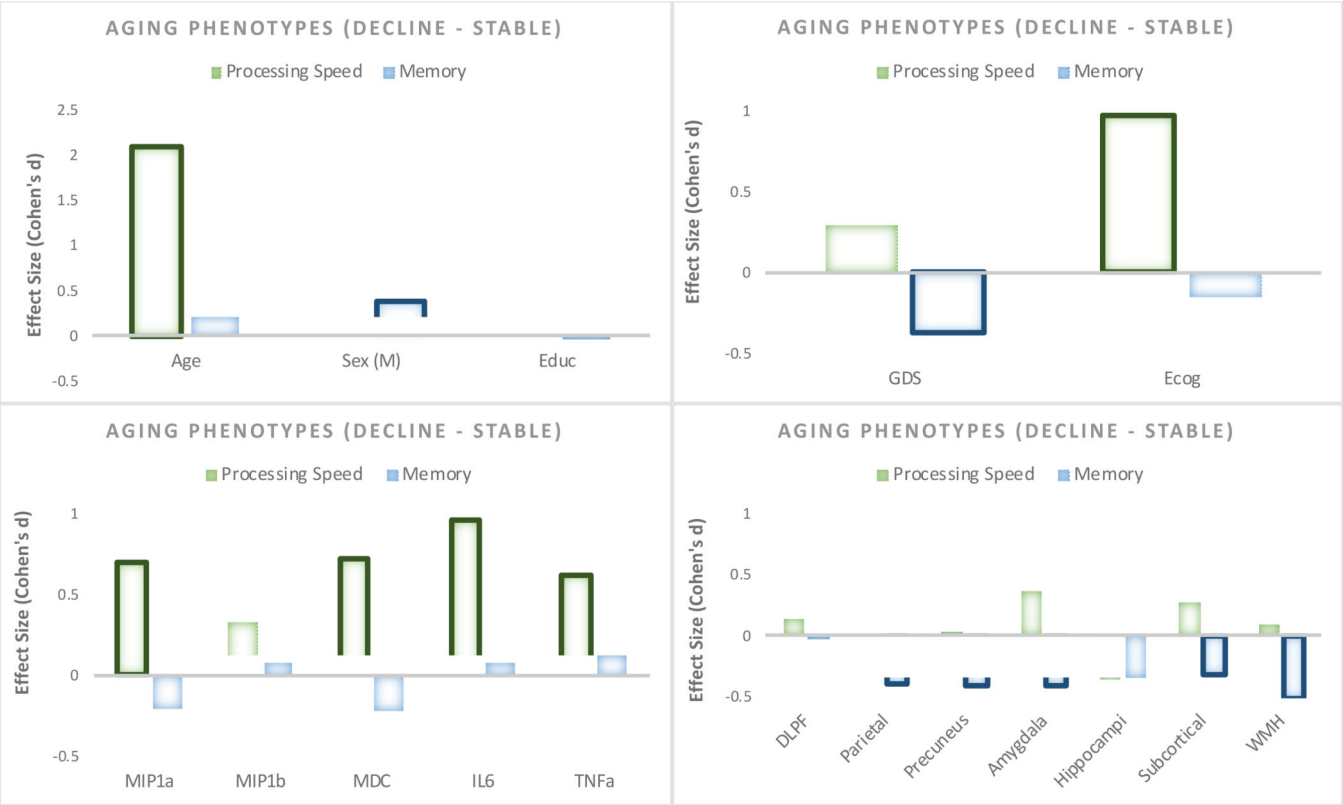

Figure 1.

Baseline characteristics uniquely discriminated older adults who developed a declining processing speed or episodic memory phenotype.

Note. Bars reflect decliners minus stable individuals such that higher effect sizes indicate that decliners have *more* of the trait; Bolded bars = $p<0.05$; All values reflect full model adjustments described in text.

Table 1.

Clinical and demographic characteristics of study participants at baseline (n=314); median (IQR) reported unless otherwise specified.

Visits	
Number of visits (mean)	4, range: 2–13
Total years in study (mean)	4.6 years, range: 1–16.5 years
Age, y (mean, SD)	69.3 (7.5), range: 47, 99
Sex, F	55.1% (173)
Education, y (mean, SD)	17.5 (2.0), range: 11, 20
MMSE	30 (29, 30)
APOEε4 (%, n)	22.5% (62)
CVLT LDFR (raw score)	12 (10, 14)
Processing speed composite (z-score)	2.2 (1.3)
Geriatric Depression Scale	2 (0, 4), range: 0, 15
Everyday Cognition Scale	1.12 (1.1, 1.4)
Cytokine markers (pg/mL)	
IL-6	0.60 (0.47, 0.91)
TNFα	2.3 (2.0, 3.0)
MDC	876.0 (712.1, 1090.3)
MIP1α	13.9 (10.5, 17.8)
MIP1β	55.7 (43.5, 69.7)
MRI Volumes (mm^3)	
Total grey matter (L^3)	0.61 (0.06)
Amygdala	1.7 (0.19)
Hippocampus	5.3 (0.53)
Precuneus	24.4 (2.9)
Parietal	89.4 (10.3)
DLPFC	12.0 (1.4)
Subcortical	15285.4 (1563.6)
White matter hyperintensities (mm^3)	2185.7 (1001.5, 4748.5)

Note. MMSE = Mini-Mental State Exam; CVLT LDFR = California Verbal Learning Test, Long Delay Free Recall; IL-6 = interleukin 6; TNF = tumor necrosis factor alpha; MDC = macrophage derived chemokine; MIP = macrophage inflammatory protein; MRI = magnetic resonance imaging.

Table 2.

Stepwise regression models identifying the best combination of baseline factors that differentiates between typically aging adults who go on to develop a declining processing speed or episodic memory phenotype.

	Entropy R^2	Misclassification Rate	AUC	Effect Likelihood Ratio (X^2)	beta estimate	Bootstrap 95% CI*	p-value
Processing Speed Phenotype (Decline vs. Stable)							
Model Fit (n=85)	0.75	0.047	0.996	74.7			<0.001
Baseline Regressors							
Processing Speed				54.2	4.3	2.46, 8.58	<0.001
TNFα (log)				10.07	4.0	0.75, 7.28	0.002
ECog				6.60	8.6	−.91, 22.87	0.01
Episodic Memory Phenotype (Decline vs. Stable)							
Model Fit (n=90)	0.28	0.14	0.84	24.7			<0.001
Baseline Regressors							
CVLT LDFR				13.6	0.50	0.19, 0.84	0.003
Sex (M=1; F=2)				6.1	−2.0	−0.17, −1.81	0.02
Precuneus volume				10.5	−0.47	−0.91, −0.05	0.005
WMH vol (log)				2.5	−0.55	−1.44, 0.16	0.11

Note.

*Bootstrapped using 1000 samples.

TNFα = tumor necrosis factor-alpha; ECog = Everyday Cognition Scale; CVLT LDFR = California Verbal Learning Test, Long Delay Free Recall (episodic memory); WMH = white matter hypterintensity.