



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



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ABSTRACT

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

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1. Introduction

Cognitive aging is a highly heterogeneous clinical phenomenon with equally diverse underlying biology. The Einstein Aging Study recently identified that up to 9 unique “cognitive classes” best fit their data in a large cross-sectional cohort of nondemented older adults using a data-driven approach (latent class modeling) (Zammit et al., 2018). Similarly, in typically aging adults followed up for 7 years in the Geneva Variability Study, Mella et al. (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. 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 β_{1-42} , TDP-43) (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 and 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, whereas frontostriatal networks better predict memory functioning in older adults; in addition, although 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 of these different mechanisms.

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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 aged >65 years is estimated to exceed that of children (United States Census Bureau, 2018); there is a huge public health need to identify clinically relevant (and potentially modifiable) factors that are associated with suboptimal 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 nonoverlapping cognitive aging phenotypes and (2) characterize *baseline* clinical and biological factors that differentiate individuals who go on to develop each phenotype.

2. Methods

2.1. Participants

Three hundred fourteen participants who completed at least 2 annual study visits as part of the University of California, San Francisco Memory and Aging Center’s healthy aging study were included. Participants represent a community-dwelling, convenience sample of the Bay Area collected between 2000 and 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 2 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 2 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).

2.2. 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 *nonoverlapping* 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 minutes) 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).

2.3. 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).

2.4. Laboratory markers of inflammation

Baseline 12-h 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 (TNF α)—and chemokine markers more specific to monocyte/macrophage activation—macrophage inflammatory protein 1-alpha (MIP1 α ; CCL3), macrophage inflammatory protein 1-beta (MIP1 β ; CCL4), and macrophage-derived chemokine (MDC). We chose IL6 and TNF α given their known involvement in multiple proinflammatory 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.

Table 1

Clinical and demographic characteristics of study participants at baseline ($n = 314$)

Visits	
Number of visits (mean)	4, range: 2–13
Total years in study (mean)	4.6 y, range: 1–16.5 y
Age, y (mean, SD)	69.3 (7.5), range: 47–99
Sex, female	55.1% (173)
Education, y (mean, SD)	17.5 (2.0), range: 11–20
MMSE	30 (29, 30)
APOE ϵ 4 (% , 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)
TNF α	2.3 (2.0, 3.0)
MDC	876.0 (712.1, 1090.3)
MIP1 α	13.9 (10.5, 17.8)
MIP1 β	55.7 (43.5, 69.7)
MRI volumes (mm ³)	
Total gray 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	15,285.4 (1563.6)
White matter hyperintensities (mm ³)	2185.7 (1001.5, 4748.5)

Median (IQR) reported unless otherwise specified.

Key: CVLT LDFR, California Verbal Learning Test, Long Delay Free Recall; IL6, interleukin 6; MMSE, Mini–Mental State Examination; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; MRI, magnetic resonance imaging; TNF, tumor necrosis factor alpha.

2.5. 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 Mini–Mental State Examination, memory, or processing speed performances compared with those who did not receive. Notably, there were more males who completed neuroimaging ($p = 0.005$), which we adjusted for in all imaging-related models.

2.5.1. Acquisition parameters

Participants completed a 3T Magnetom Vision TIM Siemens Trio system (Siemens, Iselin, NJ, USA) magnetic resonance imaging scan within 180 days of their neuropsychological evaluation. A T1-weighted magnetization prepared rapid acquisition GRE structural scan was acquired with an acquisition time of 8 minutes 53 seconds, sagittal orientation, a field of view of $160 \times 240 \times 256$ mm with an isotropic voxel resolution of 1 mm^3 , repetition time = 2300 ms, echo time = 2.98 ms, time inversion = 900 ms, and flip angle = 9° .

2.5.2. 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 nonlinear and rigid-body registration. Images were smoothed using an 8-mm Gaussian kernel with 8-mm full width half maximum. For registration with a brain parcellation atlas, linear and nonlinear 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 was estimated for each subject in MNI space.

2.5.3. 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).

2.5.4. White matter hyperintensity volumes

White matter hyperintensities (WMHs) 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 the Expectation Maximization software (Avants et al., 2011; Dadar et al., 2017).

2.7. Statistical analyses

2.7.1. 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 16th percentile (corresponding with -1 SD on a normal curve) of the sample as “decliners,” whereas those with slopes in the upper 84th percentile were classified as “stable” on the given measure (Heaton et al., 2004). It is important to note that although we derived a -1 SD “declining” cutpoint within our sample, these data represent an independently functioning cohort of clinically normal older adults overall—that is, these individuals are simply at the outlying ends of the normal curve (not “impaired”). We elected to classify individuals into groups (vs. 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 cutoff approach to allow for calculation of more clinically meaningful predictive parameters (e.g., classification rates).

2.7.2. Baseline predictors

Once the phenotypes were defined, we conducted analysis of covariance 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 versus stable phenotypes into a forward, combined direction stepwise logistic regression model with a minimum Akaike information criterion (AICc) stopping rule.

3. 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”), whereas 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”), whereas 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. 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 with speed-stable adults. After adjusting for baseline processing speed, older age at baseline significantly differentiated between speed-declining versus speed-stable individuals ($b = 2.6$, $p = 0.003$). There were no significant group differences on sex ($\chi^2 = 0.10$, $p = 0.75$) 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 ($b = 0.29, p = 0.003$), TNF α ($b = 0.10, p = 0.047$), MIP1 α ($b = 0.14, p = 0.03$), and MDC ($b = 0.12, p = 0.02$) as well as endorsed more cognitive symptoms at baseline (ECog; $b = 0.05, p = 0.04$) compared with speed-stable adults. The speed phenotypes did not differ on baseline MIP1 β 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 gray matter ROIs (p 's > 0.30), WMH volumes ($b = 0.05, p = 0.82$), or APOE $\epsilon 4$ ($\chi^2 = 0.17, p = 0.68$) (Fig. 1).

We then entered age, baseline processing speed, IL-6, MIP1a, MDC, TNF α , and ECog scores as possible regressors into our final stepwise model. The best fitting model (Bayesian information criterion = 26.6, AICc = 17.5, $X^2(3) = 74.74, p < 0.001$) included baseline processing speed, TNF α , and perceived cognitive symptoms (see Table 2). These 3 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.

3.2. Episodic memory phenotype

At baseline, individuals who went on to evidence a declining memory phenotype demonstrated better memory performances at their first visit compared with 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; $\chi^2 = 4.5, p = 0.03$); 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 WMH burden ($b = -0.25, p = 0.049$) compared with 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, whereas 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 with 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 to -0.02 ; p 's > 0.55) or APOE $\epsilon 4$ ($b = -0.02, p = 0.93$) (Fig. 1).

We entered baseline memory, sex, parietal, precuneus, amygdala, and WMH volumes and GDS as possible regressors into our final stepwise model. The best model (Bayesian information criterion = 85.0, AICc = 73.3, $X^2(4) = 24.7, p < 0.001$) included baseline memory, sex, precuneus, and WMH 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 memory-stable phenotype.

4. Discussion

In a cohort of comprehensively evaluated, high-functioning older adults, we found evidence for distinct cognitive aging trajectories with *nonoverlapping* biological and clinical characteristics at baseline. Although 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

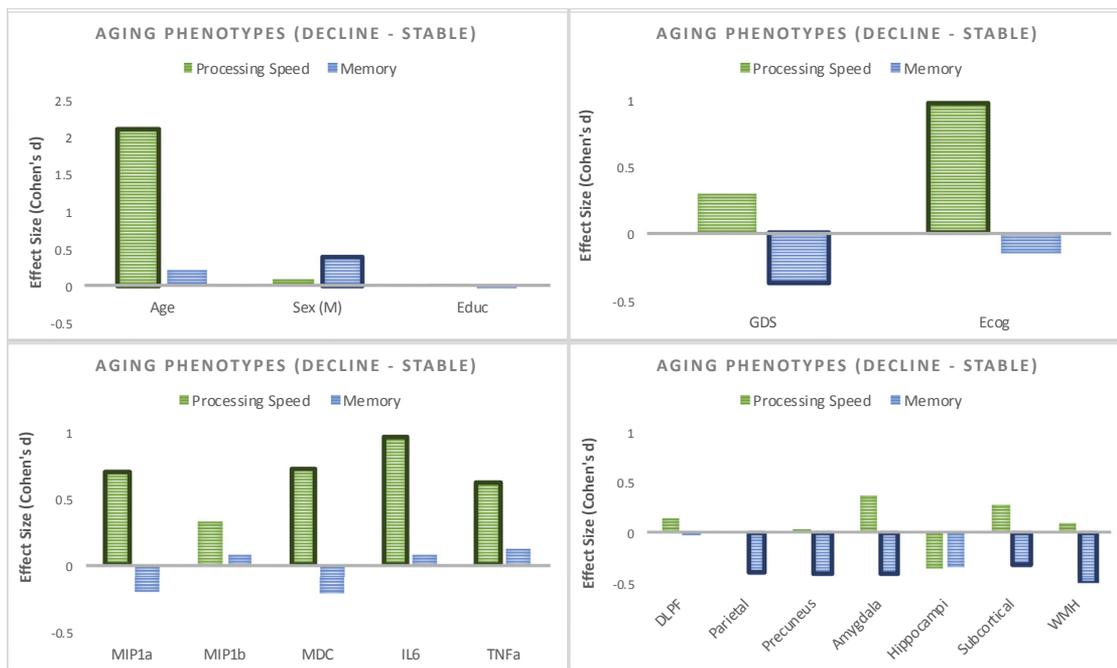


Fig. 1. Baseline characteristics uniquely discriminated older adults who developed a declining processing speed or episodic memory phenotype. Bars reflect decliners minus stable individuals such that higher effect sizes indicate that decliners have *more* of the trait; Bolded bars = $p < 0.05$. All values reflect full model adjustments described in text. Abbreviations: DL PF, dorsolateral prefrontal cortex; ECog, Everyday Cognition Self-Report Scale; GDS, Geriatric Depression Scale; IL6, interleukin 6; TNF, tumor necrosis factor alpha; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; WMH, white matter hyperintensity.

Table 2

Stepwise regression models identifying the best combination of baseline factors that differentiate 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 ^a	p-value
Processing speed phenotype (decline vs. stable)							
Model fit (n = 85)	0.75	0.047	0.996	74.7			<0.001
<i>Baseline regressors</i>							
Processing speed				54.2	4.3	2.46, 8.58	<0.001
TNF α (log)				10.07	4.0	0.75, 7.28	0.002
ECog				6.60	8.6	-0.91, 22.87	0.01
Episodic memory phenotype (decline vs. stable)							
Model fit (n = 90)	0.28	0.14	0.84	24.7			<0.001
<i>Baseline regressors</i>							
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 volume (log)				2.5	-0.55	-1.44, 0.16	0.11

Key: AUC, area under the curve; CVLT LDFR, California Verbal Learning Test, Long Delay Free Recall (episodic memory); ECog, Everyday Cognition Scale; TNF α , tumor necrosis factor-alpha; WMH, white matter hyperintensity.

^a Bootstrapped using 1000 samples.

went on to develop a speed- or memory-declining phenotype. Older age, endorsement of psychological distress, and immune activation differentiated between speed-declining versus speed-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 that 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.

Although 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 cutpoints (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 Alzheimer’s disease [AD]). However, particularly in the 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 on the dynamic nature of cognitive aging and, given their unique characteristics, provides insight into points for at-risk monitoring and primary prevention to support healthy 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, although 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 mechanisms 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. Although 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 individuals with a 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 processing speed impairment and 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 et al. (2017) demonstrated

heightened peripheral inflammation in adults with treatment refractory depression and 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 than 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 than females (Jack et al., 2015). Although the pathways are not fully delineated, sex chromosomes appear to play an important and possibly mechanistic role in animal models. Dubal et al. (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). In addition, 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, although 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 frontotemporal 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. Although some of our results are consistent with findings thus far in more diverse samples (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) selected a cohort of older adults who were clinically normal at baseline and followed up 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 mild cognitive impairment or were A β + 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. Although 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 is 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.

Disclosure

The authors have no actual or potential conflicts of interest.

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