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Cognitive Aging and Dementia: A Life-Span Perspective

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Abstract

This review summarizes empirical findings and theoretical concepts in cognitive aging and late-life dementia research, with emphases on (*a*) person-to-person heterogeneity in trajectories of cognitive change over time, (*b*) how trajectories of child cognitive development determine peak levels of adult cognitive function from which aging-related cognitive declines occur, and (*c*) how lifelong trajectories of cognitive function relate to the timing of severe cognitive impairments characteristic of dementia. I consider conceptual issues surrounding categorical versus dimensional models of late-life dementia and discuss how current diagnostic approaches affect inferences in the empirical study of disease progression. Together, the incomplete current understanding of the biological foundations of aging-related cognitive declines and the continuous nature of many biomarkers commonly used in dementia diagnosis and classification pose both opportunities and challenges in the current research landscape. Future research will benefit from accurately measuring and analyzing continuous variation in longitudinal trajectories of cognitive function.

Contents

INTRODUCTION

Research in cognitive aging seeks to identify and understand the risk factors, determinants, mechanisms, and sequelae of aging-related cognitive declines and late-life dementia. In this review, I highlight key themes and findings from this field, emphasizing overarching conceptual issues. One area of focus is the importance of understanding person-to-person heterogeneity in trajectories of cognitive change over time. A second area of focus is the need to distinguish risk factors and correlates of late-life cognitive function and dementia that differentiate trajectories of cognitive decline over the course of adulthood from factors that differentiate trajectories of cognitive growth over the course of childhood. A third area of focus is how lifelong trajectories of cognitive function relate to the timing of severe cognitive impairments characteristic of dementia. Finally, I discuss whether dementia and its pathophysiological bases are best conceptualized and measured as categorically distinct processes from those underlying normative aging-related cognitive changes or rather as extreme regions of continuous distributions of changes that occur in the population with age. I begin by introducing key concepts, definitions, and epidemiological patterns in cognitive aging and dementia research.

DEFINITION, CORRELATES, AND STRUCTURE OF COGNITIVE FUNCTION

Cognitive function is an umbrella term that encompasses many different distinct cognitive abilities. These include the abilities to efficiently and accurately solve abstract problems (fluid reasoning), quickly carry out mental operations (processing speed), mentally rotate and manipulate objects (spatial ability), maintain information in consciousness while simultaneously updating or manipulating information (working memory), encode and retrieve information (episodic memory), acquire knowledge from experience (learning), accurately recite and apply cultural information (crystallized knowledge), and carry out learned procedures and operations (procedural knowledge). What characterizes all cognitive abilities is that they reflect capabilities to optimize performance, for instance, in terms of speed, efficiency, and/or accuracy. Importantly, measures of

cognitive function are remarkably predictive of real-world outcomes, even though everyday life does not typically demand that individuals perform at levels at which they are maximally capable (Cronbach 1949) and many cognitive abilities are measured using abstract tests that do not superficially resemble the everyday demands of the real world. Cognitive abilities have been robustly linked with educational outcomes, socioeconomic attainments, health, and longevity (Gottfredson & Deary 2004, Deary et al. 2010). In fact, a composite measure of cognitive abilities has been described as the single "best predictor of job performance" (Ree & Earles 1992; see also Schmidt & Hunter 1998), and performance on cognitive ability tests has been strongly linked with everyday functions among older adults, such as medication use, financial management, and food preparation (Diehl et al. 1995, Allaire & Marsiske 2002). Very low cognitive abilities are associated with lower quality of life, limited functional independence, and substantial economic costs (CDC 2004). It has been suggested that the reason that cognitive abilities are robustly related to such a diverse array of real-world outcomes is that they measure the ability to deal with complexity, and that complexity is itself crucial for navigating society writ large (Gottfredson 1997).

Notwithstanding the distinctions between them, individual differences in different cognitive abilities measured in the general population at a single point in time are positively intercorrelated. In other words, individuals who have strengths in one cognitive domain tend to have strengths in other cognitive domains, and those who have weaknesses in one domain tend to have weaknesses in other domains. Spearman (1904) was the first to document this positive manifold of interrelations among different cognitive variables, inferring that they arise because all cognitive variables rely partly on the same general intelligence factor (which he termed *g*), in addition to specific factors (which he termed *s*) that affect only the individual variables. Contemporary factor analytic taxonomies of cognitive abilities (Carroll 1993, McGrew 2009) expand on this idea, featuring factors underlying highly specific cognitive functions, factors influencing broader ability domains, and a general intelligence factor underlying all cognitive abilities. The "universally found statistical regularity" (Plomin & Deary 2015) of positive correlations among cognitive abilities has been documented from infancy through old age (Tucker-Drob 2009, Cheung et al. 2015), yet debate remains regarding the interpretation of this pattern and whether it is sufficient evidence that the *g* factor is anything more meaningful than a statistical dimension of covariation (e.g., van der Maas et al. 2006, Kovacs & Conway 2016). Even if interpreted only as a statistical dimension, the *g* factor may have great utility for parsimoniously summarizing individual differences in performance on many different cognitive tests. On average, *g* accounts for approximately 40% of the variation in individual cognitive tests and approximately 60% of the variation in broad ability domains (Carroll 1993).

THE EPIDEMIOLOGY OF COGNITIVE AGING

In the general population, average levels of cognitive function increase normatively across childhood, peak at some point in adulthood, and decline into old age. The overall shape of these population-average trajectories differs across abilities. Cognitive abilities that require predominantly effortful processing at the time of assessment (e.g., fluid reasoning, visuospatial ability, episodic memory, and processing speed) typically peak in early adulthood (e.g., the twenties) and decline monotonically throughout middle and late adulthood, whereas cognitive abilities that rely predominantly on recital or rote application of previously acquired knowledge (e.g., crystallized knowledge, procedural knowledge, and specialized professional skills) typically peak in late adulthood (e.g., the sixties) and begin declining only at advanced ages (Cattell 1971, McArdle et al. 2002). Following Cattell (1971), it is common to refer to the former as fluid abilities and the latter as crystallized abilities. This distinction, however, has the potential to confuse these

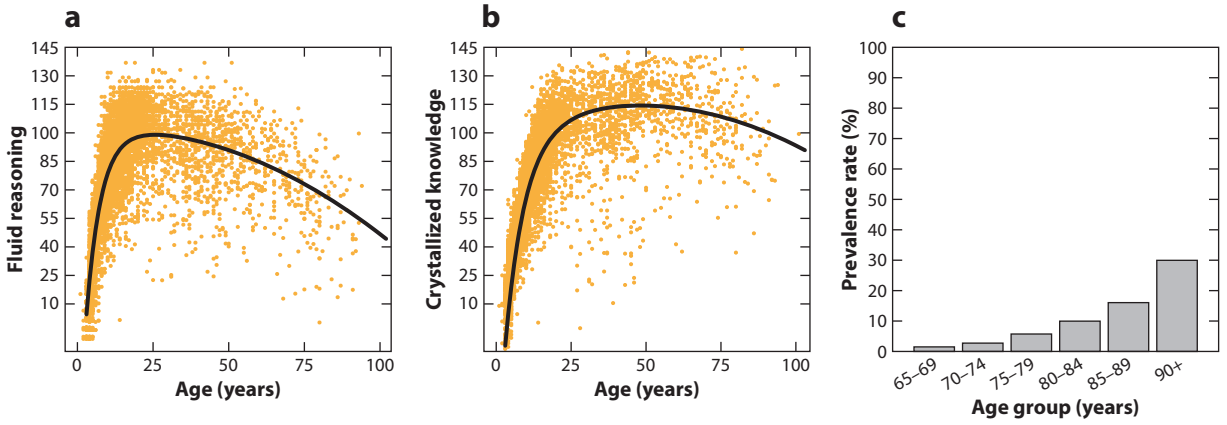

Figure 1

Cross-sectional age trends in (*a*) fluid reasoning, (*b*) crystallized knowledge, and (*c*) dementia prevalence. Data on fluid reasoning ($N = 5{,}712$) and crystallized knowledge ($N = 5{,}315$) are from the *Woodcock–Johnson Tests of Cognitive Abilities*, Third Edition (Woodcock et al. 2001). Both fluid and crystallized abilities have been scaled such that the mean and standard deviation of performance between ages 18 and 21 years are 100 and 15 units, respectively. Dementia prevalence rate statistics are from the Medical Research Council Cognitive Function and Ageing Study II ($N = 7{,}720$; Matthews et al. 2013).

inclusive category labels with the fluid reasoning and crystallized knowledge ability domains that exist alongside other ability domains, such as processing speed, episodic memory, and spatial visualization. Alternative terms for those abilities requiring primarily effortful processing versus those abilities requiring primarily previously acquired knowledge are cognitive mechanics versus cognitive pragmatics (Baltes 1987), or process abilities versus product abilities (Salthouse 1988). Cross-sectional age trends in fluid reasoning and crystallized knowledge, as exemplars of process and product abilities, respectively, are displayed in **Figure 1*a*** and ***b***. Note that in the remainder of this review, I present stylized plots resembling the trends observed for process abilities, but many of the same concepts that I describe apply equally well to the patterns observed for product abilities.

Cross-sectional estimates of age trends in cognitive function are known to be confounded by cohort differences (Baltes et al. 1977). In other words, higher cognitive performance among more recently born individuals could inappropriately contribute to an impression of steeper cognitive declines with advancing age in cross-sectional data. Indeed, cross-sectional estimates tend to indicate steeper rates of aging-related cognitive declines than are indicated by conventional longitudinal studies (Baltes & Schaie 1974). Conventional longitudinal estimates of cognitive aging, however, suffer from biases associated with practice effects (Salthouse & Tucker-Drob 2008) and selective attrition (Lindenberger et al. 2002), typically in the direction of underestimating rates of cognitive decline over time (Horn & Donaldson 1976). Overall, studies that have corrected cross-sectional data for cohort effects and longitudinal data for practice and attrition have tended to be in closer agreement, converging on declines in process abilities beginning in early adulthood and gains in product abilities through early and middle adulthood (Rönnlund & Nilsson 2006, Salthouse 2009). Further bolstering the conclusion that normative aging-related decrements begin in early adulthood, cross-sectional patterns of monotonic aging-related declines in cognitive performance following reproductive maturity have been observed in studies of nonhuman animals (ranging from fruit flies to nonhuman primates) raised in standardized environments, for which cohort differences provide less plausible explanations. Finally, the general patterns depicted in **Figure 1*a*** and ***b*** have been observed across historical time (e.g., Jones & Conrad 1933) and cultures, including in a forager–farmer population with very limited schooling (Gurven et al. 2017).

DEFINITION AND EPIDEMIOLOGY OF DEMENTIA

Dementia, increasingly referred to as major neurocognitive disorder (NCD) (APA 2013), is an umbrella term for a syndrome, namely a constellation of co-occurring systems, of heterogeneous etiology across individuals. The cardinal symptom of dementia is cognitive deterioration that affects the activities of daily living. Distinguishing dementia from neurodevelopmental disorders, such as intellectual disability, is the loss of cognitive function. Cognitive impairments characteristic of dementia are conceptualized as distinct from those associated with delirium (which develops over a very short period of time and often fluctuates substantially over hours or days) and with other psychiatric disorders, such as depression and schizophrenia. The etiological bases for dementia are nevertheless understood to be highly heterogeneous across individuals. Some common etiological subtypes of dementia that are included in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5; APA 2013), are Alzheimer's disease (AD), frontotemporal lobar degeneration, vascular disease, traumatic brain injury, HIV infection, and Huntington's disease. The discussion in this review is most applicable to what the DSM-5 refers to as "NCDs of aging." These dementia subtypes are not typically directly attributable to infectious diseases (e.g., HIV), major Mendelian disorders (e.g., Huntington's disease), or acute physical trauma (e.g., traumatic brain injury). AD, which is characterized by cortical atrophy, amyloid-predominant neuritic plaques, and tau-predominant neurofibrillary tangles, is the major form of the dementia subtypes considered here. Dementia is often attributed to neuropathological features associated with multiple subtypes (so-called mixed etiology), especially in older adults (Schneider et al. 2007). Nevertheless, despite the common practice of classifying dementia into biologically based etiological subtypes, the biological mechanisms underlying these dementia subtypes are not well understood.

In practice, dementia is typically diagnosed using cognitive testing. Such testing often takes the form of a screening instrument, such as the Mini–Mental State Examination (MMSE; Folstein et al. 1975), that is sensitive to differences between normal-range and impaired cognitive functioning (but not sensitive to variation within the normal range of cognitive functioning). Both when dementia screening instruments are used and when more extensive cognitive testing batteries are employed, it is commonplace in dementia research to categorize scores into normative, preclinical (e.g., mildly impaired), and clinical ranges. Clinicians take into account the patient's personal history, including educational attainment and occupational history, when determining whether the impaired cognitive level represents a lifelong impairment or a decline. Dementia is typically diagnosed when cognitive function has dropped below a lower threshold, beyond which impairment of everyday functions is considered severe. Such a threshold is inherently probabilistic because dementia diagnoses are not determined by cognitive testing alone. DSM-5 guidelines further indicate that the impairment must be distinguished from "normal aging," although—as is discussed in the section titled Categorical and Continuous Models of Cognitive Aging and Dementia—the distinction between normal aging and pathological aging is ambiguous at best.

It is increasingly common practice to include neuroimaging and assay of cerebrospinal fluid biomarkers in clinical assessments for suspected dementia. These biological measurements are used for differential diagnosis, for guiding the specific dementia subtype diagnosed (e.g., frontotemporal dementia, vascular dementia, or AD), and for charting disease progression. The reliance on neuroimaging and other biomarkers in diagnosis is complicated by the imperfect scientific understanding of the etiologies of various dementia subtypes, the lack of specificity of many biomarkers with respect to associations with specific dementia subtypes and other neurological disorders, and the ambiguous distinction between normal and pathological forms of cognitive aging. Nevertheless, there have been increasing calls to base clinical diagnoses exclusively on

biomarkers, even in the apparent absence of cognitive symptoms or clinical manifestations (Jack et al. 2018). Still, low cognitive function, as indicated by cognitive testing, and deficits in abilities to complete activities of daily living, which often stem directly from low cognitive function, continue to be the driving factors in dementia diagnoses in both clinical and research settings. As I discuss throughout this review, reliance on a cognitive performance threshold for dementia diagnosis has given rise to fundamental ambiguities in much of the existing empirical body of literature in this area.

As displayed in **Figure 1*c*** for a recent study from the United Kingdom, dementia prevalence rates in Western industrialized populations have been estimated to increase from approximately 1% among 65-year-olds to approximately 30% among individuals older than 90 years of age (Lobo et al. 2000, Matthews et al. 2013). Dementia incidence rates have similarly been estimated to increase with adult age, from approximately 5 new cases per 1,000 person-years at age 65 to approximately 80 new cases per 1,000 person-years at age 90 (Matthews et al. 2016). A meta-analysis indicates that dementia incidence rates double approximately every five years of advancing age between 65 and 90 (Jorm & Jolley 1998), with one study of Americans older than 90 years indicating that this trend continues past age 100 (Corrada et al. 2010). Overall, incidence rates may yield a more accurate representation of dementia risk by age, as they are less confounded by associations between dementia risk and longevity. Nevertheless, as is the case for cross-sectional estimates of continuous age gradients in cognitive function, age-comparative analyses of both prevalence and incidence rates of dementia may be confounded by cohort effects. Indeed, there is evidence for decreasing dementia risk among later-born cohorts (Matthews et al. 2013, 2016). Whether dementia screening instruments and cognitive testing criteria should be recalibrated on the basis of cohort trends in cognitive abilities is an open question (cf. Kanaya et al. 2003).

PERSON-TO-PERSON HETEROGENEITY IN RATE, SHAPE, AND TIMING OF COGNITIVE DECLINES

Population average trends, by their very nature, represent the aggregation of individual trends across people. **Figure 2** depicts a heuristic plot of the population-average trajectory and eight stylized person-specific trajectories for one exemplar cognitive ability across the life span. In this figure, childhood and adolescence are characterized primarily by age-related increments in cognitive function, whereas adulthood is characterized primarily by age-related decrements. However, each person's trajectory is unique. Some individuals make rapid increases through childhood, and others experience relatively slow increases during this period. Some individuals continue to increase into adulthood, whereas others peak in their cognitive performance in adolescence. Some individuals maintain relatively high levels of cognitive function into old age, whereas others experience rapid aging-related declines in cognitive functions. In other words, shapes and rates of developmental increases, ages at peak cognitive function, levels of peak cognitive function, and the shapes and rates of subsequent aging-related declines vary across individuals (McArdle et al. 2002, McArdle & Wang 2008). As shown in **Figure 3**, these trajectories lead to differences in the ages at which children attain a level of cognitive function needed for independent daily function, as well as the ages at which adults drop below the level of cognitive function needed to continue to live independently (Hertzog et al. 2008, Tucker-Drob & Salthouse 2011).

That individuals differ from one another in their trajectories of life-span cognitive development and declines suggests that the relative ordering of individuals changes from one point in time to the next. Indeed, longitudinal research indicates that, just as mean rates of cognitive change are most pronounced in childhood, the reordering of individuals relative to one another is most pronounced in childhood. Meta-analysis indicates that the longitudinal stability of cognitive

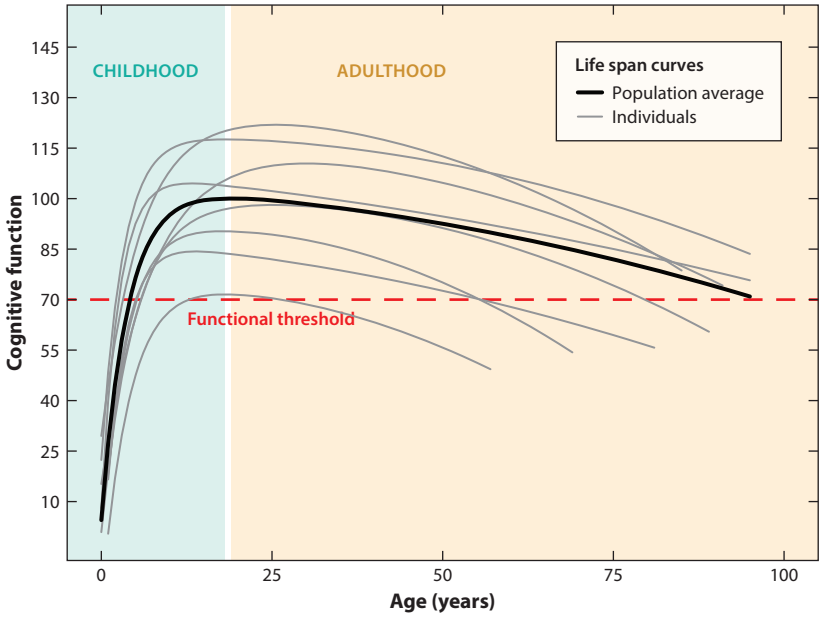

Figure 2

A stylized representation of life-span curves for cognitive function for individuals (*thin gray lines*) and the population average (*thick black line*). Individual curves vary in the age at which they cease in order to represent person-to-person variation in age at mortality. The dashed red horizontal line represents a functional threshold, below which cognitive function is too low for the typical individual to function independently in everyday life. All individuals begin life below this functional threshold, and typically developing individuals surpass it over the course of childhood. As individual cognitive function declines over the course of adulthood, some individuals drop back below the functional threshold. These individuals are often diagnosed with cognitive impairment or dementia. In this plot, cognitive function has been scaled such that the mean and standard deviation of performance in early adulthood are 100 and 15 years, respectively. In this hypothetical example, the functional threshold of 70 is approximate and is likely to vary across assessment protocols. Simulated data.

abilities (r) increases dramatically from approximately 0.3 over a six-year period in early childhood to approximately 0.8 over such period by late adolescence (Tucker-Drob & Briley 2014). Thus, although individuals reorder to some extent at all points in the life span, the most dramatic reordering per unit of time is in childhood. In older age, as trajectories of cognitive aging increasingly diverge, r may decrease.

How do individual differences in aging-related changes in different cognitive abilities relate to one another, if at all? As put by Rabbitt (1993), "Does it all go together when it goes?" Indeed, just as there is a positive manifold of correlations among individual differences in different cognitive abilities at a single point in time, a recent meta-analysis of longitudinal studies indicates a positive manifold of correlations among rates of aging-related changes in different abilities (Tucker-Drob et al. 2019). In other words, adults who decline, for example, more steeply than their same-age peers in their processing speed are also likely to decline relatively more steeply in their episodic memory and visuospatial ability. On average, a general factor accounts for 60% of the variability in cognitive changes, and this factor of longitudinal changes is itself strongly linked with longitudinal changes in everyday functions (Tucker-Drob 2011a). Consistent with the hypothesis that "an ensemble of common sources increasingly dominates development of intellectual abilities" (de Frias et al. 2007, p. 382), the pattern is more pronounced at older ages: A general factor of

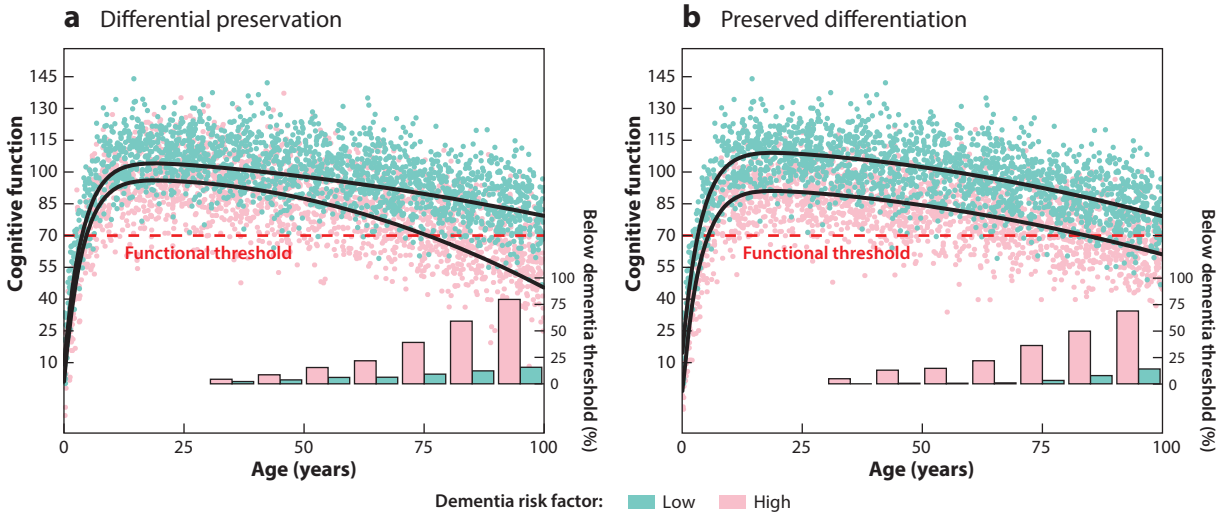

Figure 3

Two stylized scenarios representing how a dementia risk factor may operate with respect to cognitive aging. (*a*) This scenario represents what Salthouse et al. (1990) have termed "differential preservation," whereby low- and high-risk groups differentially preserve their cognitive function with advancing adult age. (*b*) This scenario represents what Salthouse et al. (1990) have termed "preserved differentiation," whereby the differences observed between low- and high-risk groups are preserved across adulthood. Both scenarios lead to differences in the rate of dementia diagnosis by level of the risk factor (as indicated by the inset bar graphs). In these plots, cognitive function has been scaled such that the mean and standard deviation of performance in early adulthood are 100 and 15 years, respectively. The inset bar graphs represent the proportion of individuals within each 10-year age group with cognitive scores below the functional threshold beyond which dementia diagnosis is likely, stratified by level of the dementia risk factor. In these hypothetical examples, the functional threshold of 70 is approximate and is likely to vary across assessment protocols. Simulated data.

change accounts for approximately 45% of the variance in changes at age 35 years, increasing to approximately 70% by age 85 years (Tucker-Drob et al. 2019). This pattern is observed even among studies that carefully control for dementia.

INTERPRETING CORRELATES OF ADULT COGNITIVE FUNCTION AND DEMENTIA RISK

An individual's cognitive function at any point in time represents a terminal state of the trajectory of cognitive change up until that point. For example, as illustrated in **Figure 2**, an individual may reach a low overall level of cognitive function in late adulthood either because she has declined substantially and precipitously from a previously high peak state of cognitive function (attained via rapid or prolonged gains during childhood, adolescence, and possibly early adulthood) or because she has gradually and modestly declined from a relatively low peak state of cognitive function (attained via shallower or foreshortened gains during childhood and adolescence), or some combination of the two. Whether an individual's cognitive function has dropped below a functional threshold results—to different extents for different individuals—from a combination of the peak level of cognitive function previously attained and the magnitude of subsequent decline from that peak. Indeed, for some individuals presenting with dementia, impairment may be attributable primarily to shallow trajectories of childhood cognitive development, rather than particularly steep trajectories of adult cognitive declines. These facts add complexity to the interpretation of correlates of adult cognitive function and late-life dementia risk.

Salthouse (2006) and Salthouse et al. (1990) have distinguished between two stylized patterns by which a correlate of late-life cognitive function and dementia risk might relate to cognitive function over the life span. The first pattern is termed differential preservation: the tendency for individuals with different levels of a risk factor to differentially preserve their cognitive function with adult age. Under this scenario, those low in the risk factor exhibit relatively shallow average rates of aging-related cognitive declines, whereas those high in the risk factor exhibit relatively steep average rates of aging-related cognitive declines. The simulated data in **Figure 3*a*** illustrate this pattern for high- and low-risk subpopulations. As the figure demonstrates, individuals within each subpopulation vary around the age-specific subpopulation mean, such that some individuals within the lower tail of each subpopulation distribution fall below the functional threshold beyond which dementia diagnosis is likely. As mean levels of performance of the high-risk subpopulation decrease rapidly with advancing adult age, the rate of dementia diagnosis for this subgroup increases markedly. In contrast, as mean levels of performance of the low-risk subpopulation decrease slowly over the same period, the rate of dementia diagnosis for this subgroup increases only modestly. This pattern of differential preservation is likely the pattern that usually comes to mind when observing patterns of differential dementia risk across levels of an observed variable.

The second pattern by which a risk factor for late-life cognitive impairment might act over the life span is termed preserved differentiation: the tendency for the differences in cognitive function that are associated with a risk factor to emerge by early adulthood and be preserved over the course of aging. Under this scenario, those high in a risk factor, compared with those low in that factor, exhibit lower average levels of cognitive function in early adulthood but similar average rates of subsequent aging-related cognitive declines. The simulated data in **Figure 3*b*** illustrate this pattern for high- and low-risk subpopulations. Again, individuals within each subpopulation vary around the subpopulation mean, such that the cognitive function of individuals within the lower tail of each subpopulation distribution falls below the functional threshold. As mean levels of performance for both high- and low-risk individuals decrease equally with advancing adult age, the rates of dementia diagnosis for both subgroups increase, albeit substantially more markedly for those in the high-risk subgroup. The difference in dementia risk by subgroup is not attributable to differential rates of cognitive aging, but simply to the fact that the high-risk subgroup's mean is closer to the functional threshold at all points in adulthood. This pattern of preserved differentiation is often not considered in attempts to account for differences in dementia risk by levels of an observed variable, although it may often be the most appropriate explanation of the data. However, the distinction between differential preservation and preserved differentiation is fundamental to understanding a wide range of correlates of late-life function and dementia risk, whether biological, social, or lifestyle related in nature. The distinction allows researchers to understand whether the risk factor is associated with rate of cognitive development, rate of cognitive decline, or a combination of the two.

A textbook example of a dementia risk factor that operates through a differential preservation pattern is the *APOE* genotype. Polymorphisms within the *APOE* gene are robustly associated with late-onset AD (Liu et al. 2013) in the direction of higher risk among carriers of the *E4* allele. Whereas this observation alone is insufficient for concluding that *APOE* is a risk factor for aging-related cognitive decline (i.e., differential preservation), evidence spanning a wide range of studies has confirmed this to be the case. In an early longitudinal cohort study, Deary et al. (2002) found that IQ scores at age 11 years were unrelated to *APOE* genotype, whereas by age 80 years there was a significant difference between groups, in the direction of lower performance among those with the *E4* allele compared to those without it. There was also a significant association between *APOE* genotype and magnitude of cognitive change between ages 11 and 80 years, in the direction of more negative change associated with the *E4* allele. Several more recent studies have

reported associations between *APOE* genotype and longitudinal rates of aging-associated cognitive declines specific to later adulthood. For instance, in data from participants measured at ages 70, 73, and 76 years, Ritchie et al. (2016) reported associations between *APOE* genotype and a general factor of longitudinal cognitive changes across multiple ability domains in the direction of steeper cognitive change among carriers of the *E4* allele. Finally, in a meta-analytic sample ($N = 53{,}949$), Davies et al. (2015) reported that a single-nucleotide polymorphism (SNP) located within the *APOE* region of the genome was related to general cognitive function at genome-wide significant levels ($p < 5 \times 10^{-8}$), but this effect varied substantially with age of the contributing cohort ($r = -0.424$). A cross-sectional meta-regression model indicated that at cohort mean age equal to 55 years, the SNP is unrelated to general cognitive function, with the absolute magnitude of the effect increasing linearly with cohort mean age, through 80 years. In other words, the difference in cognitive performance across individuals differing in *APOE* genotype increased with age, indicating differential preservation of cognitive function by *APOE* genotype.

An example of a dementia risk factor that operates primarily through a preserved differentiation pattern (despite common wisdom to the contrary) is low educational attainment. The inverse association between educational attainment and dementia risk has been well known for some time (Katzman 1993) and has led to long-standing debates regarding whether the association results from bias of diagnostic tests against low-education groups, delayed onset or slower progression of pathophysiology underlying dementia, or so-called reserve processes in which pathophysiology is less strongly linked to cognitive function among the well educated due to greater tolerance, redundancy, or compensation (Stern et al. 1994). Xu et al. (2016) reported meta-analytic evidence for a dose–response relation between educational attainment and dementia risk, in the direction of a 7% decrease in dementia risk per year of additional educational attainment. Such findings, however, are insufficient for distinguishing between differential preservation and preserved differentiation patterns with respect to educational attainment and cognitive aging. Studies that have examined associations between educational attainment and longitudinal changes in continuously distributed variation in cognitive performance are dispositive. Several carefully conducted studies of this sort (e.g., Van Dijk et al. 2008, Tucker-Drob et al. 2009, Zahodne et al. 2011, Ritchie et al. 2016; also see the meta-analysis by Seblova et al. 2019) have consistently documented associations between educational attainment and levels of cognitive function but have found no evidence for an association between educational attainment and rates of aging-related cognitive declines. It remains possible that a small relation between education and rates of cognitive aging exists, such that studies several orders of magnitude larger would be needed to detect it. Such an effect by itself, however, would be too small to explain the association between educational attainment and dementia risk. Thus, the most plausible explanation for this pattern is not that educational attainment is protective against aging-related cognitive declines but rather that it is associated with the rate of cognitive development during childhood and adolescence, such that high educational attainment is associated with higher cognitive function throughout adulthood (i.e., preserved differentiation). Indeed, recent research in genetics has indicated that polygenic propensity for educational attainment is related to the rate of cognitive development over childhood (Belsky et al. 2016) but not to the rate of cognitive aging in adulthood (Ritchie et al. 2019). Moreover, a recent meta-analysis (Ritchie & Tucker-Drob 2018) of evidence from natural experiments indicates that the educational attainment–cognitive ability link is at least partly attributable to a causal effect of education on cognitive development.

Thompson (1954) and Owens (1959) have asked, "Is age kinder to the initially more able?" In other words, is peak level of cognitive function in early adulthood related to the rate of aging-related cognitive decline? This is an important question, because the answer will help determine whether researchers in cognitive aging are likely to benefit from examining correlates of levels of

cognitive abilities as risk factors for cognitive declines. Evidence from longitudinal studies of adult cognitive aging indicates that the answer to Thompson's (1954) and Owens's (1959) question is no. The meta-analytic correlation between levels of cognitive abilities and rates of longitudinal cognitive changes has been estimated at $r = 0.047$ (standard error = 0.049, $p = 0.347$; Tucker-Drob et al. 2019). Such results suggest that it is unlikely for strong correlates of levels of cognitive function to exhibit sizable differential preservation patterns. Correlates of rates of cognitive aging, that is, risk factors displaying differential preservation patterns, are likely to be different from those that are consistently related to lifelong levels of cognitive function, as is the case with respect to *APOE* genotype.

MEASUREMENT AND INFERENCE IN COGNITIVE AGING

The statistical properties of the instruments used to measure cognitive function complicate both cross-sectional and longitudinal research seeking to document, predict, or otherwise study individual differences in the rate of cognitive aging. Measurement instruments should faithfully and precisely index cognitive function to equal extents for all intended examinees. In the context of cognitive aging research, however, it is common to use both cognitive assessments and rating scales with uneven sensitivity to variation across the full range of cognitive functioning, most often in the direction of poor sensitivity to variation in the upper range of cognitive functioning. The most severe instance of this issue is a ceiling effect in which individuals with ability levels higher than a particular threshold all receive the highest score on the measure. For instance, the MMSE is on a 30-point scale, with scores below 30 in the below average to very low range of functioning. Individuals whose cognitive functioning is above average are likely to receive a 30, regardless of whether they are slightly above average or very high above average. This leads to a compression of the MMSE distribution at the upper range of functioning. Even in the absence of ceiling effects, tests that are composed of fewer difficult items (items sensitive to differences in the high range of functioning) than easy items (items sensitive to differences in the low range of functioning) often produce a similar, albeit less severe, compression of the distribution at the upper range of functioning.

Instruments with poor sensitivity to the upper range of cognitive functioning produce particularly pernicious biases when used to chart trajectories of cognitive function with age. This is because, when such instruments are employed, mean declines in performance with age cause the distribution to expand as it moves away from the region of poor measurement sensitivity (i.e., the ceiling), thereby producing spurious patterns of differential preservation (**Figure 4**). For example, in a longitudinal study of more than 2,000 individuals, Dufouil et al. (2000) report that the tenth to ninetieth percentile interquantile range of MMSE scores increased by a factor of two between the ages of 75 and 95 years, increasing from 21–29 at 75 years to 10–27 at age 95 years. Such dramatic increases in variance with adult age are not observed in representative studies that have employed cognitive tests sensitive to the full range of functioning (Woodcock et al. 2001, Salthouse 2004), indicating that they are an artifact of poor measurement.

A heuristic way of conceiving of this problem is to envision that, even though the maximum possible MMSE score is 30, some individuals have true—albeit unobserved—scores well above this ceiling level. An individual who has declined 10 points from a true score of 30 will show a 10-point decrement from 30 to 20, whereas an individual who has declined 10 points from a true score of 35 will show only a 5-point decrement from 30 to 25, and an individual who has declined 10 points from a true score of 40 will show no decrement on the MMSE. Thus, the MMSE may produce an apparent pattern of less decline among individuals with initially higher true ability levels in early adulthood. Any correlate of early adulthood ability levels (e.g., educational attainment, childhood

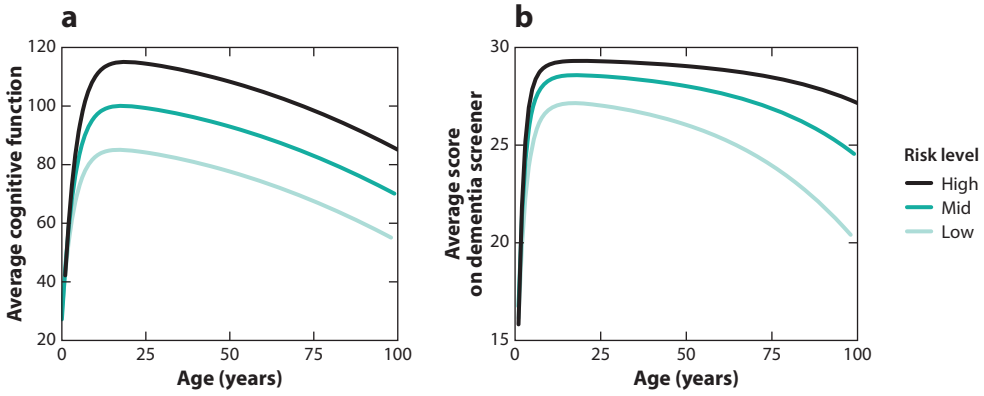

Figure 4

Plots of (*a*) average cognitive function by age and (*b*) average scores on a dementia screening instrument by age, stratified by an early childhood risk factor for dementia (e.g., childhood socioeconomic status). Both plots are based on the same set of simulated data. Data were generated such that the risk factor was related only to rate of childhood cognitive development, not to rate of aging-related cognitive change. Scores on the dementia screening instrument were derived directly from cognitive function scores using a transformation to reflect lower test sensitivity at higher levels of cognitive function. The dementia screening instrument gives the misimpression of differential preservation, that is, that the risk factor is related to the rate of aging-related cognitive decline. Simulated data.

socioeconomic status, or total brain volume in early adulthood) is likely to produce the appearance of a differential preservation pattern with respect to MMSE scores (or scores on similarly crude instruments). Differential preservation has been observed empirically, for example, with respect to associations between educational attainment and longitudinal MMSE change (e.g., Lyketsos et al. 1999), even when preserved differentiation is observed with respect to educational attainment and changes in more sensitive cognitive measures, as reviewed in the preceding section. In sum, whereas carefully conducted studies using sensitive cognitive measures indicate no evidence that age is "kinder to the initially more able," studies using dementia screeners give the incorrect impression of a positive association between baseline cognitive function (and its correlates) and subsequent aging-related cognitive changes.

CATEGORICAL AND CONTINUOUS MODELS OF COGNITIVE AGING AND DEMENTIA

A long-standing goal in cognitive aging research has been to distinguish the contributions of pathological processes from those of normative degenerative processes to aging-related cognitive declines. Indeed, the DSM-5 indicates that NCDs should be distinguished from normal aging, while speculating that "a substantial fraction of what has been ascribed to normal aging likely represents prodromal phases of various NCDs" (APA 2013, p. 609). The categorical model of dementia, as distinct from normative aging that is implicit in this directive, is portrayed for two hypothetical individuals in **Figure 5**, which attributes total decline in cognitive function relative to peak levels in early adulthood to a combination of normative and pathological sources. Under this model, an expected trajectory of potentially shallower decline for any given individual can be envisioned under a counterfactual scenario of no pathology.

A key point illustrated in **Figure 5** is that the contribution of pathology to cognitive decline may begin long before an individual reaches the threshold of cognitive function beyond which

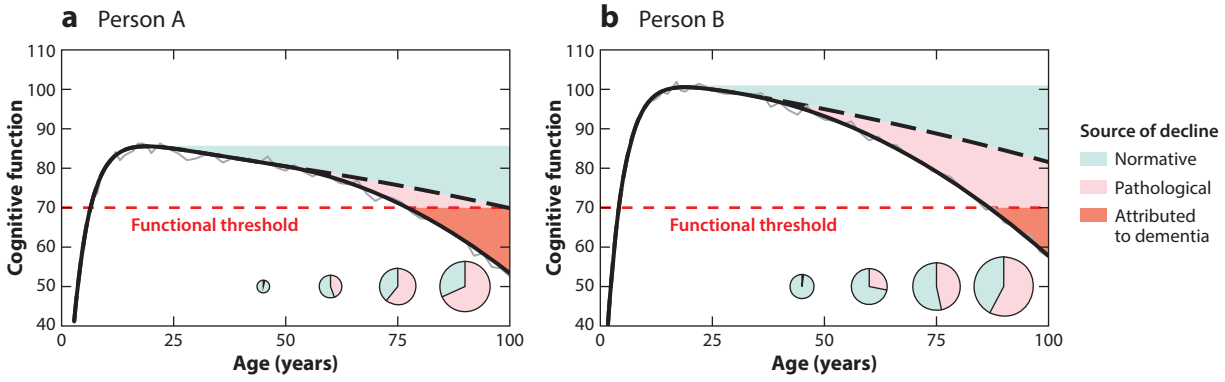

Figure 5

A categorical model of pathological aging projected onto simulated data for two hypothetical individuals. The solid black lines represent the realized trajectories in cognitive function for (*a*) person A and (*b*) person B, whereas the dashed black lines represent the expected trajectories in cognitive function for these individuals under a counterfactual of no pathology. The dashed red lines represent the threshold of cognitive functioning beyond which dementia diagnosis is likely. The light aqua shaded regions indicate the total amount of change from peak performance that is attributable to normative processes, the light pink shaded regions indicate the amount of additional change from peak that is attributable to pathological processes, and the red shaded regions indicate the amount of change in cognitive function beyond the dementia threshold. The inset sequences of pie charts indicate the relative amount of change during each 15-year period of adulthood attributable to normative versus pathological sources. The size of each pie is scaled to reflect the total amount of cognitive change occurring during the respective 15-year period. Simulated data.

a dementia diagnosis is likely. In the case of AD, for example, it is widely recognized that "the pathophysiological process of [AD] begins years, if not decades, before the diagnosis of dementia" (Sperling et al. 2011, p. 281). This observation has led some researchers (Sperling et al. 2011) to prioritize distinguishing between the pathophysiological processes underlying AD and the clinically relevant cognitive and behavioral manifestations of AD, and has led others (Jack et al. 2018) to advocate for an exclusively biological definition of AD. Jack et al. (2018), for example, recommend that the field work toward defining AD from biomarkers falling within three core groups: β-amyloid deposition, pathologic tau, and neurodegeneration. Factors complicating such an approach are incomplete knowledge of the full set of biological processes underlying AD pathology, the possibility that the known AD biomarkers are particularly inappropriate for staging the early phases of AD pathology progression, and the lack of specificity of some biomarkers with respect to AD versus other neurological disorders (Dubois et al. 2014). This general issue is not specific to AD but likely applies to a host of late-life dementia subtypes.

Nevertheless, it is useful to consider how a categorical model of cognitive aging and dementia may intersect with current practices for diagnosing dementia. As discussed in the sections above, the major determinant of a diagnosis of dementia is whether an individual drops below a threshold level of cognitive function. At the time of dementia diagnosis, individuals whose peak levels of cognitive function in young adulthood were high will have declined further in their abilities than those whose peak levels were low, as is apparent in comparing the trajectories of cognitive decline for hypothetical individuals A and B in **Figure 5**. Person A's peak level of cognitive function during young adulthood is 85 points (only 15 points above the hypothetical dementia threshold), whereas person B's peak level of cognitive function during young adulthood is 100 points (30 points above the hypothetical dementia threshold). Thus, by the time person A has been diagnosed with dementia he has undergone 15 points of cognitive decline, whereas by the time person B has been diagnosed with dementia she has undergone 30 points of cognitive decline. In other words, person A and person B are at very different stages of disease progression at the time of their dementia

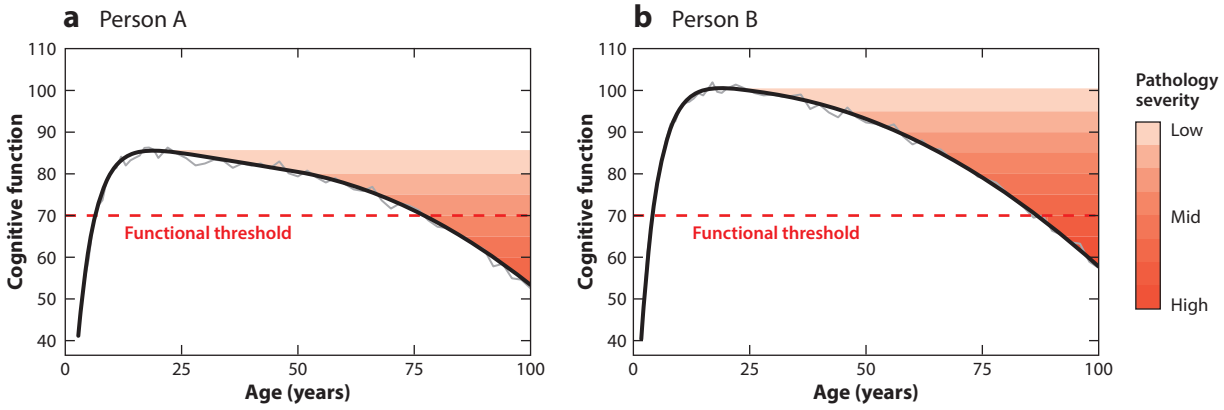

Figure 6

A continuous model of pathological aging projected onto simulated data for two hypothetical individuals. The solid black lines represent the realized trajectories in cognitive function for (*a*) person A and (*b*) person B. The shading represents the degree of pathology. The dashed red lines represent the threshold of cognitive functioning beyond which dementia diagnosis is likely. Simulated data.

diagnoses. In this example, the onset of pathological decline is much later for person A than for person B. Yet person A is diagnosed with dementia at an earlier age than person B. Person B's pathology has gone undetected for a longer period of time, not because she has staved off cognitive declines but because of the employment of an absolute cognitive function threshold for dementia diagnosis. Moreover, at the point of dementia diagnosis, person B's rate of cognitive decline is much steeper than that of person A, simply because her rate of cognitive decline is being estimated at a later stage of disease progression. Thus, using the point of dementia diagnosis as a means of staging or establishing a timescale of disease progression has the strong potential to lead to biased, often paradoxical, patterns of empirical results. Indeed, this exact pattern of differences in detection timing by peak early adulthood levels of cognitive function may explain observations that educational attainment is associated with later age of dementia onset, steeper rates of cognitive decline surrounding dementia diagnosis, and more advanced pathology progression at time of dementia diagnosis, all of which others have invoked cognitive reserve to account for (Stern 2012).

Categorical models of cognitive aging and dementia contrast with continuous models of cognitive aging and dementia, which treat the distinction between normative and pathological aging as a matter of degree rather than kind. Key to continuous models is the assumption that the etiological factors that underlie normal-range aging-related cognitive declines are the same as those that underlie the dramatic cognitive declines that are recognized as pathological. Such a model is depicted for hypothetical individuals A and B in **Figure 6**. Rather than there being a sharp distinction between normal aging and dementia, severity of cognitive decline from peak is expected to be proportional to severity of pathology. Continuous models do not presume a single form of pathophysiology, or even that the same subset pathophysiological processes is present in all individuals. Rather, continuous models predict that the causal factors underlying normal-range cognitive decline for any given individual are, in greater dose or co-occurrence, the same causal factors that underlie dementia for other individuals. For instance, mild frontotemporal atrophy may be the primary basis for normal-range cognitive declines in some individuals, whereas more severe frontotemporal atrophy, or the co-occurrence of mild frontotemporal atrophy and other independently mild neurodegenerative processes, may be the primary basis for severe cognitive deficits underlying dementia for other individuals.

In some instances, the distinction between categorical and continuous models, or lack thereof, may be a matter of perspective. For example, is the effect of mild neurovascular microinfarcts on normal-range cognitive declines evidence for a continuous model of cognitive aging and vascular dementia, or is it evidence that what are currently treated as normal-range cognitive declines are in fact the early stages of disease progression? Answers to such questions are likely to differ across dementia subtypes. When the key biomarkers of pathology for a dementia subtype vary continuously within the population of adults at large, and this variation is continuously related to cognitive function (as is likely to be the case for neural atrophy), a continuous model of cognitive aging and dementia may be most appropriate. Alternatively, when the key biomarkers of pathology for a dementia subtype are present at detectable levels in only a subset of individuals, and/or a nonzero association between biomarkers and pathology is present only beyond a certain biomarker level, a categorical model of cognitive aging and dementia may be most appropriate. For some dementia subtypes, key (potentially yet-to-be-identified) biomarkers are likely to consist of a combination of continuously and categorically distributed indices (cf. Jack et al. 2013), in which case the distinction between normal and pathological sources of cognitive aging will be blurry at best. Of course, further progress in the identification and understanding of dementia biomarkers has the potential to lead to changes in dementia subtype nosology.

As is the case for categorical models of cognitive aging and dementia, continuous models of cognitive aging and dementia may produce paradoxical patterns of results when intersecting with current threshold approaches for dementia diagnosis. As illustrated for the two hypothetical individuals in **Figure 6**, the same age at dementia diagnosis will be associated with different degrees of pathology severity for different individuals as a function of their peak levels of cognitive function in early adulthood. Ceteris paribus, individuals who have lower peak ability levels will tend to be diagnosed with dementia at earlier ages and at lower levels of pathology severity than will those who have higher peak ability levels. Thus, just as is the case for categorical models of cognitive aging, using point of dementia diagnosis on the basis of current threshold approaches as a means of staging or establishing a timescale of disease progression has the strong potential to lead to biased, often paradoxical, patterns of empirical results. Either type of model is likely to be sufficient to account for phenomena that others have invoked cognitive reserve to explain (Stern 2012).

CONCLUSION: TOWARD A CHANGE-BASED ASSESSMENT OF DEMENTIA

Human cognitive function changes throughout the life span, from infancy through old age. Individuals differ from one another in the timing, rates, and shape of life-span trajectories of cognitive change. Counter to the prevailing medical perspective on cognitive aging, aging-related cognitive declines are not confined only to late life, or to a small subset of the population. Although cognitive aging is often represented as a process marked by an abrupt transition to precipitous decline from a long period of fully maintained cognitive function (cf. Stern 2012), it may be more accurately represented as a continuous process of change marked by accelerated decline, for some, with advancing age. Understanding these basic facts is fundamental to research seeking to identify and understand the social, epidemiological, and neurobiological correlates, determinants, and sequelae of aging-related cognitive declines and dementia.

Inherent in current definitions of dementia is cognitive decline from an earlier peak level of cognitive function. However, current practices for dementia diagnosis often do little to quantify the magnitude of cognitive decline beyond verifying that some amount of cognitive decline has occurred, instead focusing on absolute levels of current cognitive function and activities of daily living as the primary desiderata. As described in this review, these threshold-based methods for

diagnosing dementia can produce ambiguous or misleading findings across a variety of research settings. For example, such methods are inadequate for distinguishing between differential preservation and preserved differentiation as the basis for patterns of differential dementia risk, and are thus inadequate for determining whether an identified risk factor for dementia operates through associations with adult cognitive aging or child cognitive development. Moreover, such methods have the strong potential to produce strong dependencies between correlates of peak levels of cognitive function in early adulthood and pathology severity and disease progression at the time of dementia diagnosis. Finally, under a categorical model of cognitive aging and dementia, current threshold approaches may mistake normative aging for dementia at greater rates for individuals with lower peak levels of early adult cognitive function (e.g., those with lower educational attainment), potentially confounding research seeking to identify risk factors or biomarkers for pathogenesis.

Diagnosing dementia on the basis of change over time is a promising, albeit challenging, alternative for avoiding many of the issues associated with criteria that lean heavily on absolute cognitive function thresholds. Change-based diagnostic approaches may not be feasible in clinical settings in which, for a given patient, a history of cognitive function is not available, or only surrogate markers of premorbid cognitive function such as educational attainment or vocabulary are available. Nevertheless, for prospective longitudinal research seeking to identify biomarkers for, predictors of, and correlates of dementia incidence, including prospective clinical trials to deter or delay dementia, tracking continuous variation in cognitive change over time is certainly feasible and has the strong potential to produce more valid endpoints and outcome criteria. Practice effects associated with repeated measurements of individuals over time are likely to attenuate the impression of cognitive decline with age, but classifying change relative to other cohort members (in the case of an observational study) or control group participants (in the case of a randomized controlled clinical trial) with equal amounts of test experience may help reduce the effects of such confounds on the key inferences of interest (Tucker-Drob 2011b). In prospective longitudinal research in which cognitive function has been carefully and continuously measured, there is certainly no need to use a lower threshold of function to diagnose dementia. Although such a threshold may correspond to clinically relevant impaired activities of daily living, there is evidence that aging-related cognitive declines even in the normal range are closely linked with aging-related longitudinal changes in everyday functions (e.g., accurately paying bills, following medication instructions, making change, and looking up telephone numbers in a phone book; Tucker-Drob 2011a). Thus, irrespective of absolute levels of cognitive function at a given point in time, continuous measures of cognitive change over time capture meaningful variation in declines that are relevant for adults' everyday lives.

A focus on change over time is key to distinguishing whether correlates of late-life cognitive deficits represent correlates of aging-related cognitive declines or simply correlates of peak levels of cognitive function. This focus has already prompted the realization that many (though not all) of the risk factors for dementia operate largely through preserved differentiation patterns. In other words, the risk factors are robustly related to peak levels of cognitive function attained by early adulthood, but not appreciably related to rates of cognitive declines. Such results indicate that research into cognitive aging will benefit from life-span approaches (Baltes et al. 1999) that account for the developmental processes that unfold over the first two decades of human ontogeny, and that policy and intervention work may have some of its greatest impact on preventative approaches that focus on childhood and adolescence. Identifying which factors do and do not operate through associations with adult cognitive changes (i.e., differential preservation patterns as opposed to preserved differentiation patterns) will shed further light on the risk factors and biological mechanisms underlying cognitive declines proper, and will likely lead to clearer

understanding of the degenerative processes underlying the more extreme rates of accelerated decline characteristic of dementia.

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Contents

Errata

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