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Defining Cognitive Reserve and Implications for Cognitive Aging

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Abstract

Purpose of Review—The aim of this review is to summarize current conceptual models of cognitive reserve (CR) and related concepts and to discuss evidence for these concepts within the context of aging and Alzheimer's disease.

Recent Findings—Evidence to date supports the notion that higher levels of CR, as measured by proxy variables reflective of lifetime experiences, are associated with better cognitive performance, and with a reduced risk of incident mild cognitive impairment/dementia. However, the impact of CR on longitudinal cognitive trajectories is unclear and may be influenced by a number of factors. Although there is promising evidence that some proxy measures of CR may influence structural brain measures, more research is needed.

Summary—The protective effects of CR may provide an important mechanism for preserving cognitive function and cognitive well-being with age, in part because it can be enhanced throughout the lifespan. However, more research on the mechanisms by which CR is protective is needed.

Keywords

Cognitive reserve; Aging; Alzheimer's disease; Biomarkers; Cognition; Review

Introduction

As the population aged 65 years and older increases, the prevalence of dementia is expected to increase as well [1]. Although Alzheimer's disease (AD) is the most common cause of dementia and cognitive decline among older individuals [2•], other types of neuropathology are frequently seen [3-6] and make variable contributions to cognitive decline [2•]. According to recent estimates, only about 50% of inter-individual variability in cognitive decline, on average, can be explained by current measures of the most common age-related neuropathologies [2•, 7], suggesting that other factors may also impact cognitive trajectories in non-demented individuals. In light of this, and the lack of effective treatments for

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dementia, research is increasingly focusing on identifying factors that may delay the onset of cognitive impairment or impact cognitive outcomes. One such factor is the concept of *cognitive reserve* (CR), a theoretical construct used to describe individual differences in susceptibility to cognitive, functional, or clinical decline due to aging or brain disease [8•].

Defining Cognitive Reserve

The concept of cognitive reserve grew out of the observation that there can be discrepancies between the amount of neuropathology present in the brain and the degree of cognitive or functional impairment among individuals [9, 10]. Although there has been much research on cognitive reserve and related concepts, the term has been defined and used in different ways across studies, research teams, and consensus papers.

Cognitive Reserve, Brain Reserve, and Brain Maintenance

A recent whitepaper published by 31 members of the Reserve, Resilience, and Protective Factors Professional Interest Area, established with the support of the Alzheimer's Association, defines CR as "adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult." [8•] This framework postulates that lifetime experiences, in combination or interaction with genetic factors, enable cognitive processes to be resilient by influencing the efficiency, capacity, or flexibility of brain networks, which allow individuals to better cope with brain disease or aging. These experiences include educational and occupational attainment, general cognitive ability or intelligence, and engagement in activities that are cognitively, socially, and physically stimulating. This framework differentiates cognitive reserve (defined above) from the concept of *brain reserve*, which refers to the structural characteristics of the brain at a given point in time (e.g., premorbid brain volume, white matter integrity) and may protect against age and disease-related brain changes by impacting the threshold at which cognitive or functional decline emerge. The related concept of *brain maintenance* refers to the process of maintaining or perhaps enhancing the brain through lifetime experiences and their interaction with genetic factors [11]. It encompasses the reduced development of age- or disease-related brain changes (e.g., reduced atrophy over time or preservation of task-related networks) and reduced pathology accumulation over time (e.g., fewer white matter hyperintensities (WMH)). These three processes collectively are thought to operate throughout the lifespan and provide individuals with "resilience" to brain aging, disease, or insult.

Resistance and Resilience

Another conceptual framework specifically proposed for the study of preclinical Alzheimer's disease suggests two general mechanisms: resistance and resilience [12•]. The concept of *brain resistance* refers to "the brain processes underlying the ability to better resist pathology" and is measured by absent or lower than expected AD pathology levels. *Brain resilience* is defined as the ability to cope with AD pathology and is measured by better-than-expected cognitive performance, brain structure, or function given some level of AD pathology. As such, the notion of brain resistance is similar to the concept of brain

maintenance in the Stern et al. whitepaper [8•], while brain resilience overlaps with the notion of cognitive reserve.

Scaffolding Theory of Aging and Cognition

According to the Scaffolding Theory of Aging and Cognition (STAC) [13], an individual's level of cognitive functioning in adulthood is determined by biological aging, genetic factors, and life experiences, via their effects on the brain, as well as by "compensatory scaffolding," which refers to neural processes that reduce the negative impact of brain aging on brain function and cognition. Similar to the Stern et al. [8•] model, it is postulated that certain life experiences (like education or physical activity) and genetic factors can enhance aspects of brain function and structure (which is similar to promoting brain reserve and brain maintenance), and can enhance the capacity for compensatory scaffolding (which is similar to promoting cognitive reserve), while other factors (like smoking, obesity, and genetics) have negative effects on brain health. The model further postulates that some of the brain mechanisms that support compensatory scaffolding in aging are the same as those used among younger adults under conditions of cognitive and behavioral challenge.

Maintenance, Reserve, and Compensation

Another recent consensus paper published by Cabeza and colleagues [14•] differentiates between reserve, maintenance, and compensation. In this framework, *reserve* refers to the improvement of brain anatomic or physiological processes involved in cognition (such as the efficiency or capacity of neural processes) above current levels; thereby attenuating the effects of age- or disease-related brain changes, while *maintenance* refers to the preservation of these processes over time through ongoing cellular, molecular, and systems-level repair and plasticity. It is hypothesized that both reserve and maintenance can be influenced by genetic and environmental factors, like education, exercise, or intelligence. The concept of *compensation* is defined as the recruitment of neural processes in response to high cognitive demand that enhances cognitive performance. Compensation may be evident in response to age- or disease-related brain changes and, by definition, leads to improved cognitive performance. Although compensation, as defined in this way, appears similar to the concept of cognitive reserve in the Stern et al. [8•] framework, it is viewed as a set of distinct process (i.e., upregulation, selection, and reorganization) that may be differentially related to measures of reserve or age- and disease-related brain changes.

Residual Approach

Another approach to CR, referred to here as the "residual approach," defines cognitive reserve (or resilience) as the variance in cognition that is not explained by known (i.e., measured) brain variables and demographics [15]. Using this approach, one or more measures of brain structure, function, or pathology, in conjunction with demographic variables, are used as predictors in a model with a cognitive outcome (such as a memory score), and cognitive reserve is measured as the model residual (i.e., unexplained variance). With this approach, the measure of cognitive reserve is, by definition, dependent on the variables in the model and will necessarily differ across studies (for examples, see [15-17,

18•]). Using this residual framework, brain reserve (or brain resilience) has been defined as the residual variance in brain structure not explained by measures of AD pathology [16] or age [18•].

Defining Cognitive Reserve: Common Themes

Despite the different terminology and approaches to measuring reserve, all models seem to agree that certain lifetime experiences, in combination or interaction with genetic factors, can positively or negatively impact (a) brain health (broadly defined; including but not limited to structure, function, vasculature, metabolism, neurochemical transmission, and onset of or rate of pathology accumulation) and (b) the ability of the brain to cope with aging and pathology. The models also appear to agree that as pathology levels or age-related brain changes increase, the ability of the brain to cope with these changes decreases (i.e., level of cognitive reserve [19, 20•], brain resilience [12•], ability for compensatory scaffolding [13], and amount of residual variance [15]). For the sake of consistency, we will use the terms “cognitive reserve,” “brain reserve,” and “brain maintenance,” as defined in the Stern et al. whitepaper, throughout the remainder of this article; however, it is important to note that the evidence discussed has similar implications for the related frameworks reviewed above.

Theoretical Predictions for the Effects of Cognitive Reserve

From a theoretical standpoint, a higher level of CR is thought to impact cognitive and clinical outcomes in multiple ways. Stern’s [19] hypothetical model of CR, for example, hypothesizes that the adaptability provided by higher levels of CR are associated with (1) a higher level of cognitive performance prior to the onset of cognitive decline, as well as (2) a delay in the onset of disease-related cognitive decline. However, because individuals with high levels of CR are thought to be able to compensate for, and therefore sustain, greater amounts of neuropathology, higher levels of CR are also hypothesized to be associated with (3) a faster rate of cognitive decline once neuropathology reaches a level severe enough to impact cognitive functioning. This hypothetical model was originally developed to explain reserve-related differences in cognitive trajectories as a function of the accumulation of AD neuropathology, though it might also account for differences in cognitive trajectories due to the accumulation of other pathologies or other age-related brain changes.

Evidence for Cognitive Reserve

Because cognitive reserve is a theoretical construct, it cannot be directly observed. It is therefore most commonly measured using proxy variables that are descriptive of lifetime experiences, including measures reflective of: educational and occupational attainment, intelligence, level of engagement in lifestyle or leisure activities (e.g., socially, physically, and cognitively stimulating activities); socioeconomic status (SES); and early life experiences (including perinatal and postnatal factors, childhood intelligence, and early life SES). These variables are not mutually exclusive, often overlap, and may continue to be enhanced throughout the lifespan (for a life course model of CR, see [21]). For example, individuals who grow up in wealthier families are more likely to obtain higher levels of

education, which may lead to higher occupational attainment, greater income, and greater access to leisure activities. Examining the relative contributions of different CR proxies to risk of cognitive impairment is an active area of research [22-25]. Of note, the literature reviewed below is focused on measures of CR as it relates to aging and AD dementia. However, the concept of CR is applicable to other neurodegenerative diseases [26-29], psychiatric conditions [30-33], traumatic brain injury [34-36], and post-operative delirium [37•, 38, 39], among others.

Epidemiological and Longitudinal Cohort Studies: Cognitive Reserve Proxies and Risk of Mild Cognitive Impairment and Dementia

Epidemiological and longitudinal cohort studies are uniquely positioned to evaluate the impact of CR on longitudinal cognitive and clinical trajectories, including future risk of dementia; therefore, the below evidence for CR focuses primarily on data from longitudinal studies. The most commonly used proxy variable of CR is years of education and there is considerable evidence that more education is associated with a lower risk of incident mild cognitive impairment (MCI) [40] and dementia [41-44], though not all studies have found these relationships (for reviews and meta-analysis, see [45, 46]); results may also depend on how education is operationalized [47•]. Although easy to measure, years of education do not capture the quality of learning. Additionally, years of education is a static variable that is unlikely to change after early adulthood and thus does not capture lifelong learning and individual differences in the level of engagement in other types of stimulating activities. For these reasons, it has been suggested that literacy, reading ability, or vocabulary may be better proxy measures of reserve [48, 49]. Consistent with this proposal, measures of literacy, reading, or vocabulary tend to show stronger associations with risk of MCI or dementia than years of education [48-52].

Higher occupational attainment or work complexity have also been associated with reduced dementia risk ([53-60], but see [61]), with some data suggesting that certain types of work-related cognitive activity are more protective than others, including information processing and pattern detection [60]. Similarly, older age at retirement was found to be associated with a reduced risk of dementia [62], suggesting that lifelong cognitive engagement is beneficial. Related to occupational complexity, measures of SES, such as greater household income and wealth, have been linked to lower dementia risk [63•, 64-66].

Reduced MCI and dementia risk has furthermore been associated with greater level of engagement in cognitively, socially, and physically stimulating leisure activities, such as reading, playing games, going to museums and concerts, volunteering, or playing music ([67-71], but see [72]). As reviewed by Fratiglioni et al. [73], all three lifestyle components (social, cognitive, and physical) appear to have beneficial effects on dementia risk. Notably, most activities are not one-dimensional and may be beneficial through multiple pathways: social interactions can be cognitively stimulating and physical group activities can have social and/or cognitive components (e.g., aerobics classes, tai-chi). Some studies have therefore suggested that the variety or number of activities is more important than a specific kind of activity [74].

Early life experiences and abilities have also been related to risk of late-life cognitive impairment (for a review, see [75]), and these associations may be independent of adult educational and occupational attainment [54, 76•]. For example, higher childhood school grades [54, 76•], higher scores on cognitive ability tests at age 11 [77, 78], greater childhood SES [79], and greater complexity of writing at age 22 [80] are associated with a reduced risk of dementia, while early life hardship, such as the death of parent, are associated with greater prevalence of AD dementia [81, 82]. Prenatal factors, such as small birth weight and head circumference, may also be related to dementia risk [83•]. The evidence regarding the association between bilingualism and late-life cognitive decline has been mixed, with a recent meta-analysis concluding that bilingualism does not protect from cognitive decline and dementia ([84•], also see [85]).

Taken together, there is strong evidence that higher scores on CR proxy variables are associated with lower risk of MCI and dementia. Assuming that individuals with different levels of CR accumulate neuropathology at the same rate as they age, this provides indirect evidence that those with higher CR can withstand higher levels of neuropathology before becoming symptomatic or showing functional decline, consistent with the theoretical models of reserve reviewed above.

Epidemiological and Longitudinal Cohort Studies: Cognitive Reserve Proxies and Rate of Cognitive Decline

A large body of literature supports the association between higher levels of CR, as measured by proxy variables, and level of cognitive performance among middle-aged and older adults, including years of education [85-92], occupation, and SES [58, 65, 87, 88, 93•, 94, 95•, 96, 97], and leisure activity engagement [23, 70, 71, 98, 99]. This is in line with the predictions of Stern's model [19], according to which individuals with higher levels of CR continue to perform better than individuals with lower levels of CR as they age and neuropathology develops. The Stern model of CR also predicts that because individuals with higher CR can withstand more pathology before showing cognitive or function decline, they have a delayed onset of disease-related cognitive decline. Consistent with this prediction, several studies have shown that measures of CR are associated with a later onset of MCI [99, 100•] and dementia [101] or cognitive decline [102•, 103].

However, studies examining the effects of CR on longitudinal cognitive trajectories have been mixed. Whereas some have reported reduced rates of cognitive decline among individuals with higher levels of CR [48, 49, 65, 71, 94, 97, 104-106], others have found greater rates of cognitive decline among individuals with higher levels of CR at least on some tests [90, 91, 96, 100•, 102•, 107]. Others still have reported baseline differences in cognition by level of CR, but no difference in cognitive trajectories [58, 85, 86•, 87, 88, 92, 95•, 108, 109].

Inconsistencies in prior literature on the relationship between CR and longitudinal clinical and cognitive outcomes may be influenced by a variety of factors, including subject characteristics, methodological or analytical factors, and measurement issues. For example, a large number of prior studies have been conducted among individuals who were non-

demented at baseline and likely included individuals with normal cognition as well as individuals with MCI. However, these two clinical groups may have important *baseline* differences that might confound cognitive and clinical trajectories, including differences in levels of cognitive performance, differences in levels of baseline CR [110, 111], and differences in the amount of underlying neuropathology. Some prior studies that have accounted for clinical impairment (i.e., MCI or dementia) at baseline or follow-up have found that higher levels of CR is associated with greater rates of cognitive decline after clinical symptom onset [100•, 112-114], consistent with Stern's model [19]. In contrast, level of CR appears to have less of an impact on rates of cognitive change in non-demented aging, and may instead affect cognitive outcomes by resulting in a higher level of cognitive performance (for a review, see [89], see also [99, 100•, 115]), allowing for an improved ability to tolerate the effects of gradually accumulating pathology. Prior results may also be influenced by baseline age or length of follow-up; studies conducted among middle-aged cohorts may require longer follow-up before changes become evident, and studies among older cohorts may be subject to survival effects. See Fig. 1a-c for an illustration of some of these issues.

Methodological limitations may also impact inconsistencies in the literature. As discussed elsewhere ([92, 115, 116], see also [117]), many early studies had statistical limitations that may have biased their results. Few studies [115, 118] have been powered to examine the effects of very low levels of CR, limiting the generalizability of findings to boarder populations. This may be due to methodological factors (e.g., baseline exclusion criteria) or subject characteristics (e.g., volunteer bias, resulting in samples that tend to be highly educated, and of higher SES). Additionally, measures used to index CR may also contribute to inconsistencies in prior research, given different studies collect and operationalize similar CR proxies in different ways (for a discussion, see [119]).

Lastly, epidemiologic research on CR has generally been limited by a lack of measures of underlying pathology or age-related brain changes. As such, these studies cannot directly examine whether and how measures of CR affect the association between age- and disease-related brain changes and cognitive performance, nor do they provide insight regarding the mechanisms underlying CR. Thus, studies that have incorporated biomarkers, which are considered an indirect reflection of underlying neuropathology and/or brain aging, are of particular importance in clarifying CR-related processes.

Cross-sectional Biomarker Studies

The majority of studies on CR with biomarker measures have been cross-sectional. These studies have repeatedly shown that among non-demented groups, as well as among individuals with MCI or dementia, level of CR (as measured by proxy variables) modulates the relationship between cognition or clinical status and pathology, such as amyloid [120-122] and tau [123, 124], atrophy on magnetic resonance imaging (MRI) [22, 125, 126], WMH [127, 128], metabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET) [120, 129, 130], and cerebral perfusion [131]. These findings suggest that the effects of age- and disease-related brain changes on cognition are reduced in individuals with higher

CR, although findings among cognitively normal individuals have been more mixed [122, 124, 130, 132-134].

Cross-sectional studies have also provided a good deal of support for the idea that proxy measures of CR are related to measures of neural and brain reserve, including (but not limited to) neural efficiency and capacity [125, 135•, 136, 137•], structural measures such as brain volume and white matter integrity [125, 138-140], neurotransmission [141, 142], or cerebrovascular health [143]. As an example, fMRI studies have suggested individuals with high CR may compensate for age- or disease-related brain changes by utilizing different neural mechanisms in response to task demands [144, 145]. These types of studies provide insight into the neural mechanisms underlying CR [136, 137•, 145-147], and pathways by which brain reserve may be enhanced. However, evidence for a direct association between proxy measures of CR and level of disease-related pathology is inconclusive [134, 148-158].

Cross-sectional biomarker studies, however, are limited in that they do not allow for inferences about the direction of causality for the relationship between CR, brain integrity, and cognition. Additionally, they do not allow for an examination of the degree to which proxy measures of CR modulate cognitive decline and clinical impairment in the presence of neuropathologic and age-related brain changes, and whether they directly impact rates of change in biomarkers over time.

Longitudinal Biomarker Studies

Only a small number of longitudinal studies have examined the interaction between CR and AD biomarkers on longitudinal clinical and cognitive outcomes. As recently reviewed by Soldan et al. [20•], current evidence suggests that the protective effects of CR on the risk of progression from normal cognition to MCI do not appear to differ across the observed range of amyloid levels (as measured by cerebrospinal fluid (CSF) abeta); instead, CR and abeta have additive effects on the risk of progression to MCI [40, 154, 159]. There is some evidence that as biomarkers of neuronal injury (such as CSF total tau and atrophy on MRI scans) increase, the protective effect of CR on risk of progression to MCI decreases ([151, 154]; but see [40, 153]). This may indicate that the processes that mediate the beneficial effects of CR are less effective as levels of neurodegeneration increase, or that these processes begin to break down with disease progression (for similar findings across the spectrum of AD, see [160•]). Studies among patients with MCI have furthermore shown that given similar levels of cortical thinning, those with more education remain dementia free for a longer period of time than those with less education [101]. There is also some evidence that higher levels of education buffer against the negative impact of WMH on risk of MCI and dementia [161]. In contrast, late-life leisure activities were not found to moderate the relationship between AD biomarkers and risk of progression to dementia [152] in a non-demented cohort, but to our knowledge, this issue has not been examined among individuals with normal cognition at baseline.

Among cognitively normal or non-demented groups, the protective effects of CR on *level* of cognitive performance appears to be independent of baseline levels of AD biomarkers and cerebrovascular disease [100•, 162, 163]. However, the degree to which CR proxy measures

moderate the relationship between baseline biomarker levels and rates of cognitive decline remains unclear [100•, 162, 163] and may depend on the clinical status of individuals and level of pathology. Specifically, one study found that higher CR was associated with faster cognitive decline after symptom onset among those who eventually progressed to MCI or dementia, but did not modify cognitive trajectories among those who remained cognitively normal, independent of baseline biomarker levels [100•]. Similarly, a recent study of individuals across the spectrum of AD found that when atrophy rates were low, those with higher education showed the same or less cognitive decline over time compared to those with low education. By comparison, when atrophy rates were high (i.e., in the range of that seen among individuals with dementia), participants with high education showed greater cognitive decline than those with low education. These results, taken together, are broadly consistent with Stern's hypothetical model of CR [19] and point to the importance of taking into account both baseline and follow-up diagnosis, as well as biomarker levels, when investigating CR.

Lastly, some studies have examined the relationship between CR proxy variables and rate of change in AD and other biomarkers. A number of studies have shown that among non-demented middle-aged and older adults, greater physical activity is associated with less brain atrophy over time [164•, 165, 166, 167•], though findings have been mixed [155•, 168, 169]. Greater physical fitness and social activities have also been associated with less change in white matter microstructure [167•, 170]. In contrast, studies examining associations between other proxy measures of CR (including cognitive activities, education, occupation, and literacy) among cognitively normal and non-demented participants, and rates of change in AD biomarkers or brain structural measures, have produced mixed results. While a small number of studies reported that higher levels of CR are associated with less change in CSF abeta [171] and hippocampal volume [172, 173•], other studies did not find associations between proxy measures of CR and rates of change in amyloid [154, 155•], medial temporal lobe atrophy [153, 155•, 171], FDG metabolism [155•], and CSF tau and p-tau [154]. Among participants with AD dementia, higher education has been linked to greater cortical thinning over time [174] and greater decreases in cerebral blood flow [175].

Taken together, there is some evidence that greater physical activity levels may attenuate structural changes over time among non-demented groups, including atrophy and white matter microstructure. However, there is only weak evidence that other measures of CR directly affect the rate of change of AD biomarkers or brain structure and function. Notably, current studies are limited by relatively short intervals of longitudinal biomarker collection (2–4 years on average). More research is therefore needed to determine whether CR impacts structural and pathological brain markers over longer follow-up periods.

Summary/Conclusions

Despite differences in terminology, it seems clear that CR, as measured by proxy variables, has beneficial effects on late-life cognitive and clinical outcomes. CR proxy measures seem to be most strongly associated with a higher level of cognition, which might delay the onset of symptoms of cognitive impairment, and with reduced risk of MCI/dementia, even in the presence of pathology (see Fig. 1d). There is relatively little evidence currently, however,

that CR impacts the accumulation of disease-related pathology, although there is promising evidence that greater physical activity may be associated with less decline in structural brain measures among non-demented individuals. Additional longitudinal biomarker studies, with large samples and long follow-up intervals, are needed to determine the extent to which lifetime experiences directly impact brain reserve and maintenance. Such studies may help clarify the biological mechanisms underlying the beneficial effects of CR, since these mechanisms remain poorly understood.

To the extent that higher CR protects against the onset of disease-related clinical symptoms, or the onset of age-related cognitive decline, it provides an important mechanism for preserving cognitive function in old age, even if levels of pathology are rising. Broadly speaking, the current data suggests that initiatives that improve economic, social, and educational opportunities may have far reaching consequences for cognitive and brain health with age. For example, providing older adult communities with access to learning opportunities (such as mentoring projects, lifelong learning classes, local libraries), as well as policies that promote social connectedness and physical activity (such as green spaces, swimming pools, sidewalks, and bike lanes) may promote cognitive wellbeing. According to some estimates, delaying the onset of dementia by only 5 years would amount to a 50% decrease in dementia prevalence [176]. As such, interventions that increase level of CR may improve longevity and quality of life with age. Since most CR proxies reflect modifiable experiences that can be enhanced throughout the lifespan, current evidence further highlights the importance of lifelong engagement in cognitive, social, and physical activities.

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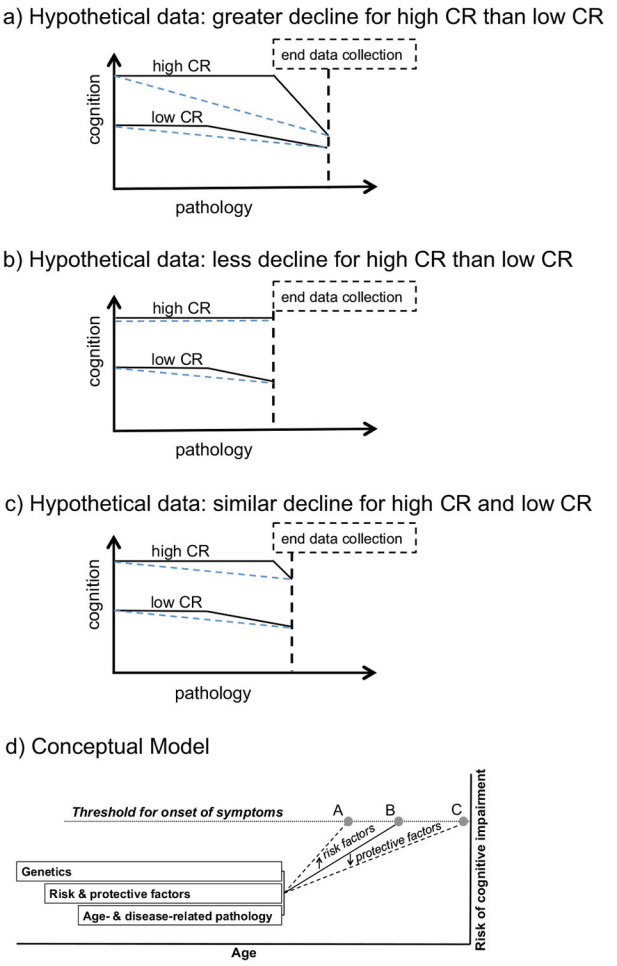

Fig. 1.

Hypothetical models illustrating the possible associations between longitudinal cognitive trajectories and pathology as a function of CR (as measured by proxy variables), based on Stern's Fig. 1 from [19]. Although the cognitive trajectories of the high and low CR participants are the same before and after onset of cognitive decline in (**a**–**c**) (as illustrated by black solid lines), the study results may differ, depending what part of the trajectory was observed (as illustrated by dashed blue horizontal lines, showing linear slopes of cognitive trajectories (**a**–**c**)). Conceptual model illustrating the lifespan impact of genetics, cognitive reserve, and age- and disease-related pathology on an individual's risk of cognitive impairment as a function of age (**d**). Evidence to date suggests that CR proxy measures impact the level of cognition (as shown by the intercept effect in (**a**–**c**)), which might delay the onset of cognitive decline (as shown by the later cognitive trajectory change point among individuals with high CR (**a**–**c**)). Evidence also suggests that CR impacts risk of cognitive impairment (as shown by points A vs. C (**d**)). While protective factors (such as high levels of CR) may move the threshold of cognitive impairment to a later age (thereby reducing risk of cognitive impairment; point C (**d**)), risk factors (such as low levels of CR, age- and disease-related brain changes, and other factors not discussed here (e.g., psychiatric conditions; poor health)) may move the threshold for cognitive impairment to a younger age (point A (**d**)). Of

note, genetics and lifestyle factors are hypothesized to act throughout the lifespan, whereas the impact of age- and disease-related pathology may not impact cognition until middle age or later. (Reprinted from: Stern, Y, *Cognitive reserve*. Neuropsychologia. 2009; 47:2015–2028; with permission from Elsevier) [19]