CHAPTER 8: RISK AND PROTECTIVE FACTORS

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Chapter 8: Risk and Protective Factors in Cognitive Aging: Advances in Assessment, Prevention, and Promotion of Alternative Pathways

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Abstract:

The chapter presents recent evidence for factors that contribute to aging-related cognitive declines, including both normal and pathological changes. The focus is on non-modifiable and modifiable risk and protective factors and their independent, multi-modal, and interactive effects on trajectories of cognitive change. Findings from long-term longitudinal studies and broad-based epidemiological investigations, as well as short-term experimental and intervention studies are considered. Moderating factors are reviewed in the context of alternative processes and outcomes, such as cognitive reserve, resilience and exceptionality. The chapter concludes with a discussion of goals to reduce or delay neurodegenerative risk and associated cognitive declines and ultimately to prevent the onset of cognitive impairment and dementia.

As the world population ages, and the national and global prevalence of Alzheimer's Disease (AD) and Related Dementias (ARD) increases dramatically, there is growing interest in understanding the processes involved in brain aging, and identifying factors that contribute to and protect against cognitive decline and impairment (Alzheimer's Association, 2016; Prince et al., 2016). It was only seven years ago that a report by the U.S. National Institutes of Health at a State-of-the Science-Conference (Daviglus et al., 2010) summarized their findings in the following way: "Firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer's Disease." In just the past several years, a remarkable amount of progress has been made in identifying the range of risk and protective factors relevant to dementia and selecting the best targets for potential intervention (Barnes & Yaffe, 2011; Livingston et al., 2017; National Academies, 2017). Given that there are still no effective pharmaceutical interventions for prevention or treatment of AD (Cummings, Morstorf, & Zhong, 2014), there has been a concerted emphasis on identifying and targeting modifiable factors that can be assessed and managed through behavioral and lifestyle changes during the long period of normal or healthy brain aging (Anstey et al., 2015). In this chapter we review the recent evidence on factors that contribute to aging-related cognitive declines, including both normal and pathological changes. The focus is on identifying non-modifiable (e.g., genotype), modifiable (e.g., lifestyle, exercise), and potentially controllable (e.g., some health conditions) factors and how they may independently or interactively modify trajectories of cognitive change prior to the insidious onset of AD. We present and integrate findings from long-term

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longitudinal studies and broad-based epidemiological investigations, as well as short-term experimental and intervention studies. Moderating factors (e.g. education, sex and gender) are reviewed in the context of alternative processes and outcomes, such as cognitive resilience and exceptionality. There is a great deal of promise in the recent findings, providing a sense of optimism that we are on the right track towards promotion of healthy brain aging and eventual delay or prevention of cognitive impairment or dementia.

Given the devastating course of ADRD and the projections for large increases in its incidence and the associated health-care costs (Hurd, Martorell, Delavande, Mullen, & Langa, 2013; Wimo et al., 2017) there has been an all-out research effort to understand the causes and to develop therapeutics targeting the underlying mechanisms. A recent report by the National Academies (2017) identified three main areas of promise for prevention of ADRD. Their recommendations were guarded, cautioning there is no clear-cut or conclusive evidence that these interventions can prevent ADRD, yet there are encouraging findings that cognitive training, blood pressure management, and physical activity may slow age-related cognitive decline. Although ADRD has received the bulk of attention and research dollars, there has been some recognition that there are also great costs associated with normal cognitive decline with aging. In 2015 an Institute of Medicine panel embarked on a review to understand normal cognitive aging as distinct from pathological cognitive changes such as those associated with impending ADRD. Their generally accepted premise was that cognitive aging is not a disease, but rather a process that unfolds throughout life and is widely experienced. The group made the following evidence-based recommendations for ways to slow cognitive changes (IOM, 2015): be physically active, reduce and manage cardiovascular disease risk factors, regularly discuss and review health conditions and medications that might influence cognitive health with a health care professional, be socially and intellectually engaged, continually seek opportunities to learn, get adequate sleep, and avoid the risks of cognitive changes due to delirium if hospitalized. Not noted, but of interest in this review, is the complementary premise that understanding pathways to resilience or sustained levels of cognitive change and plasticity in late life can provide new perspectives, targets, and opportunities for promoting healthier cognitive aging. In this chapter we elaborate on selected recent findings regarding risk and protective factors, consider mitigating and buffering factors for brain aging, and discuss emerging directions of precision assessment and intervention.

I. Risk and Protective Factors

There is growing longitudinal evidence that actual cognitive trajectories associated with normal brain aging (a) vary widely across individuals and domains, (b) include patterns ranging from relatively sustained high levels of performance to steeply accelerating decline, and (c) are influenced by individual differences in biological, health, environmental, and lifestyle factors (Josefsson et al., 2012). Arguably, the rate and extent of individual cognitive decline may not be inevitable or irreversible. In other words, there are things one can do to minimize loss in cognitive functioning and even to reduce the risks of dementia. In general, the results provide substantial evidence for brain and cognitive plasticity with normal aging. We combine the presentation of factors relevant for both dementia and normal cognitive declines, as many of the risk and protective factors are essentially the same. Indeed, given that AD is a neurodegenerative disease with a long pre-clinical onset period, virtually all known risk factors (e.g., lifestyle, genetic) and biomarkers (e.g., beta amyloid burden) are actively studied for potential contributions to early detection of elevated AD vulnerability.

Although many studies have identified significant predictors of cognition in middle and later adulthood (Agrigoroaei, Robinson, Hughes, Rickenbach, & Lachman, 2018) the evidence for factors that can delay, reduce, or reverse cognitive decline is still somewhat mixed (Plassman et al., 2010). For example, in their extensive review of both observational studies and randomized clinical trials (RCTs), Plassman and colleagues reported there are only limited benefits of cognitive training and physical exercise. They found more consistent evidence for the negative effects of risk factors such as tobacco use and disease. In recent years, this issue has attracted growing attention, with reviewers adding specific risk factors to the list. These include education, cognitive and physical inactivity, social isolation, hypertension, obesity, and environmental toxin exposure (e.g., Barnes & Yaffe, 2011). In addition to systematic reviews regarding single modifiable risk factors, some comprehensive reviews have covered a vast range of risk and protective factors associated with normal cognitive changes, impairment and dementia (Anstey et al., 2015). A 2017 Lancet Commissions article reviewed multiple modifiable risk factors and estimated the percentage of risk reduction that would occur if the major ones were eliminated (Livingston et al., 2017). Overall, the authors estimated that about 35% of the risk could be attributable to potentially modifiable factors. Figure 1 graphically represents their analysis of some of the modifiable risk factors and the fact that they operate in

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the context of unmodifiable factors. Several risk indexes have been published and some are even available online (Anstey et al., 2014).

Risk factors and protective factors are often inversely related. For example, physical activity is a protective factor for cognitive functioning. By the same token, sedentary behavior is a risk factor. On the one hand, high social support and integration are beneficial and protective, whereas loneliness and isolation are considered risk factors. Thus, with a prescriptive approach, the focus can be on reducing risk factors or increasing protective factors. In other words, the evidence indicates what to avoid and what to do to promote cognitive health. Risk assessment is an essential tool for promoting healthier brain and cognitive aging, but comprehensive assessment must be linked with strategies for risk management, risk reduction, and protection factor enhancement, strategies that are likely to involve multiple modalities (Anstey et al., 2015; Olanrewaju et al., 2015).

The modifiability of risk factors for cognitive decline and dementia varies according to onset timing, severity, proximity to brain health, propensity for interactions with other risk and protective factors, and other individualized conditions. However, some risk factors are considered non-modifiable, directly linked to brain health, and interactive with other risk factors. Perhaps most prominently are AD genetic risk loci (e.g., Apolipoprotein E, *APOE*, and the $\epsilon 4$ allele). In such cases, rather than focusing on direct interventions, it is appropriate to identify ways to moderate the effects, using a person by environment approach. That is, given the vulnerabilities, the focus can be on ways to attenuate the risks or to provide environmental supports to address them. Genetic effects and other non-modifiable factors will be presented in more detail in the section on modifiers, mechanisms, and alternative pathways.

Some of the most well-known modifiable risk factors for accelerated decline in cognitive, brain, and physical health are smoking, drug use, excessive alcohol use, and obesity. By reducing or eliminating these behaviors and conditions one can expect to improve health, reduce disease such as diabetes and heart disease, and improve cognition, or at least to slow cognitive decline and reduce the likelihood of dementia.

Health

To a large extent cognitive declines are a manifestation of general poor health (Spiro & Brady, 2011) or multi-morbidity (e.g., frailty; Searle & Rockwood, 2015) with much research linking specific health conditions to cognitive performance or change. Those who have diabetes,

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hypertension, high cholesterol, metabolic syndrome, poor lung function and other vascular and cardio-pulmonary diseases are more likely to show steeper cognitive declines than their healthier counterparts (Livingston et al., 2017). There is also evidence that if treatments for high blood pressure or diabetes and high cholesterol are effective, it can also lead to maintenance of good cognitive functioning. Thus, the longer one can remain in good health, the greater chance for maintaining good cognitive functioning.

Stress and Depression

Stress is a risk factor for poor health and cognition (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). The mechanisms have been investigated with a focus on the HPA axis and the brain. Increased stress is associated with the release of cortisol, which has damaging effects on the hippocampus (Lupien, McEwan, Gunnar, & Heim, 2009; Yaffe, Hoang, Byers, Barnes, & Friedl, 2014). Stress is also associated with increased inflammation, which also has known effects on the brain. Higher levels of inflammatory markers such as fibrinogen, CRP, or IL6 are associated with poorer cognitive performance (Karlman et al., 2014). Furthermore, stress is implicated in reduction of telomere (tips of the DNA) length, (Epel et al., 2004), which is associated with premature aging. There are many approaches to stress reduction including relaxation training, meditation, and mindfulness, with known cognitive benefits (Grossman, Niemann, Schmidt, & Walach, 2004; Zeidan, Johnson, Diamond, David, & Goolkasian, 2010). Depression, which is often comorbid with stress, has also been associated with increased risk for cognitive decline, and some of the same techniques for reducing stress are effective for treating depression. It is unclear whether depression is a risk factor per se (or an early symptom) of dementia), something that observational research continues to investigate (Dotson et al., 2010). There are some promising findings, but the jury is still out on whether these stress-reduction techniques lead to better cognitive functioning or to a reduction in cognitive decline. More work is needed to clarify the mechanisms linking stress and cognitive aging.

Environment

There is growing evidence that air pollution, pesticides, and lead exposure have negative effects on cognition (Anstey et al., 2015; Peters et al., 2015). Weuve and colleagues 2012 found that long-term exposure to particulate air pollution was associated with faster cognitive decline in the Nurses's Health Study. Exposure to toxins in the workplace (Grzywacz, Segel-Karpas, & Lachman, 2016) has been found to have a negative effect on cognitive functioning in middle-

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aged and older adults. More work is needed to clarify the particular pathways that link environmental pollutants and cognitive decline.

Behavioral and Lifestyle Factors

A number of modifiable behavioral and lifestyle factors show great promise for promoting cognitive health, and may lend themselves to developing effective interventions. Although many of the factors that are good for cognition are widely known, adults do not always behave consistently with the recommendations. For example, a majority of middle-aged and older adults in the US have poor sleep habits, are overweight or obese, or do not exercise regularly.

Sleep. Many adults have problems with sleep and this can compromise daily cognitive functioning due to fatigue. There is also evidence for long-term cumulative effects of poor sleep on cognitive functioning, especially memory (Scullin & Bliwise, 2015), and later risk of dementia (Sindi et al., 2018). There has been increased attention to treating sleep disorders and addressing difficulties that increase with age. Pharmacological remedies, both prescription and over the counter, are widely used. Such treatments do not typically solve sleep problems and they may instead contribute to poor cognitive functioning. Thus, cognitive behavioral sleep treatments may be more promising.

Diet. There are many claims about the value of dietary supplements and specific foods (Anstey et al., 2015). For example, vitamin B, antioxidants, and Omega 3's are considered helpful for cognitive functioning. Resveratrol and flavonoids, ingredients in red wine and chocolate, have received some attention. Much of this work has been done with non-human animals and the quantities needed to improve functioning in humans are unknown (Kennedy et al., 2010; Macready et al., 2009). Moreover, the large doses of wine and chocolate that would be needed to have significant effects could do more harm than good in terms of brain damage or weight gain. Thus, although these dietary ingredients may be protective, there is also evidence that obesity (body mass index) and large waist circumference are risk factors for cognitive aging and dementia. Diet plans rich in healthy fats, whole grains, legumes, fish, and produce such as the Mediterranean Diet have also been identified as beneficial for cognitive health (Lourida et al., 2013; Martinez-Lapiscina et al., 2013; Singh et al., 2014; Tangney et al., 2014; Wengreen et al., 2013). This is likely because of their effect on heart health and weight, which in turn have beneficial effects on cognition.

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Physical Exercise. There is compelling evidence that an active lifestyle has broad benefits for cognitive, physical, and psychological health (Kohl et al., 2012; Marioni et al., 2015; Powell, Paluch, & Blair, 2011). An active lifestyle can include participation in a wide range of activities -- cognitively challenging tasks, social interactions, volunteer or paid work, hobbies, and physical exercise, all of which have some health benefits. Both everyday physical activity (often moderate in extent and degree) and physical exercise (including regimens of aerobic or resistance training) have been linked to numerous health benefits, including improved cardiovascular and respiratory health, enhanced insulin sensitivity, heightened bone and muscle strength, improved positive affect and cognitive function, and increased resistance to type 2 diabetes, cancers, and depression (e.g., Corder, Ogilvie, & Sluijs, 2009; Kohl et al., 2012; Powell et al., 2011). Both moderate or everyday physical activity and exercise training have been shown to reduce stress and depression, which affect cognitive functioning. Although the benefits of regular physical exercise are well known, based on a recent report from the U.S. National Center for Health Statistics, only a small percentage of adults engage in regular physical activity (Ashe, Miller, Eng, & Noreau, 2009), and the numbers are lower for middle-aged and older adults (Thorp, Owen, Neuhaus, & Dunstan, 2011). About 20% of adults met the 2008 U.S. Center for Disease Control physical activity guidelines, and in older age groups, the percentage was lower (Clarke, Norris and Schiller, 2017). Inactivity is a global problem; the World Health Organization reported that 1 in 4 adults were not sufficiently active (World Health Organization; 2017).

Maintaining physical activity throughout life is an important public health objective (Corder et al., 2009) that is within reach with the right kind of interventions. In fact, physical inactivity has been called a global pandemic and is cited as one of the leading causes of death (Kohl et al., 2012). Physical exercise is perhaps the most well-known protective factor for cognitive aging. This has been substantiated in longitudinal, epidemiological studies as well as in clinical trials (Kramer, Erickson, & Colcombe, 2006). For example, Gow, Pattie, and Deary (2017) found that engagement in leisure physical activities in midlife was positively associated with cognitive ability level (path coefficient = .32), and higher physical activity in later adulthood was associated with less cognitive decline (.27). Moreover, the results of exercise have been found in non-human animals as well as humans. More so than other factors, there is promising evidence as to mechanisms linking physical exercise with cognition (Northey,

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Cherbuin, Pampa, Smee, & Rattray, 2017). These include increased oxygenation to the brain, brain derived neurotrophic factor (BDNF; Hillman, Erickson, & Kramer, 2008), and neurovascular integrity (Laitman & John, 2015).

There is limited evidence as to what types or amounts of exercise are needed to produce cognitive benefits, but with growing attention to the efficacy of everyday or moderate doses (Thibeu et al., 2016). Some have suggested that only aerobic activity with cardiovascular benefits is necessary for cognitive benefits (Erikson, Hillman, & Kramer, 2015). In other cases, there is evidence that resistance training has benefits for memory (Neupert, Whitbourne, & Lachman, 2009). In a study by Sofi et al. (2011), subjects who performed at low, moderate or high levels of physical activity were protected against cognitive impairment to a significant degree. Physical activity has dose-response associations with cognitive function, and even low physical activity frequencies (a few times per month) are positively associated with cognitive function during aging (de Souto Barreto, Delrieu, Andrieu, Vellas, & Rolland, 2016). Low intensity walking is related to increased hippocampal volume and reduced risk of AD (Varma, Chuang, Harris, Tan, & Carlson, 2015). One type of exercise, Tai Chi, has been particularly effective, in part because it is a multifaceted regimen that focuses on both body and mind (Wayne et al., 2014). Perhaps the biggest challenge tied to physical exercise is to find ways to motivate adults to engage in it (Sullivan & Lachman, 2017). This is one reason that researchers are also examining every day, voluntary, and safe forms of physical activity preferred by older adults (Robinson et al, 2017) that can be integrated into daily routines.

Cognitive Activity. There is evidence that cognitively-stimulating activities are associated with better cognitive functioning and less decline (Hertzog, Kramer, Wilson, & Lindenberger, 2008). Some have implemented formal training programs which show effects on the abilities that were trained, but little evidence for generalization or transfer across abilities. One exception is the ACTIVE program, which has shown long-term effects of the training over 10 years with an impact on activities of daily living and everyday functioning (Rebok et al., 2014). In other cases, there is a focus on everyday activities such as reading, doing puzzles, using computers, or learning new skills such as quilting or digital photography (Lachman & Agrigoroaei, 2010; Park et al., 2014; Small, Dixon, McArdle, & Grimm, 2012). Regardless of the particular strategy used, what still remains to be determined is how these activities get into the brain to enrich cognitive functioning, and whether they can slow or reverse declines. A

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plausible alternative explanation is that those who have better cognitive functioning are the ones who are more likely to engage in cognitive activities. Thus, more work is needed to address such directionality issues.

Another approach uses brain training games that are commercially available. The claims of companies that market these games are often exaggerated and are not based on systematic research (Stanford Center on Longevity, 2014). A review by Simon, Yokomizo, and Bottino (2012) concluded that these commercial games have little benefit beyond improvement on the tasks that are specifically practiced. Indeed, the issue of transfer effects (beyond the targeted cognitive process) is a perennial challenge to cognitive intervention studies. Moreover, the evaluations rarely use experimental designs; participants are not blind to conditions and are subject to demand characteristics. One company, Posit Science, incorporated the useful field of view training from the ACTIVE trial into their brain training program (Ball, Beard, Roenker, Miller, & Griggs, 1988), which has had some promising results, including recent findings tied reducing the risk of AD (Edwards & Loprinzi, 2017).

Cognitive stimulation in the workplace contributes to good cognitive functioning (Grzywacz et al., 2016). Occupations that involve complex decision-making and greater decision latitude, allowing for control over schedule and priorities, are tied to better cognitive functioning (Andel, Vigen, Mack, Clark, & Gatz, 2006; Andel, Kåreholt, Parker, Thorslund, & Gatz, 2007; Schooler, 1999). More work is needed in this area to tease apart selection effects, as those who have better cognitive functioning are more likely to work in more complex jobs.

Social Activity. Social activity and support have been shown related to cognitive functioning in adulthood and old age (Brown et al., 2017; Fried et al., 2004; Foubert-Samier et al., 2014; Haslam, C., Cruwys, Milne, Kan, & Haslam, S.A., 2016; Seeman et al., 2011). Cognitively stimulating leisure activity was found to be positively related to subsequent cognitive functioning especially among those with lower education (Litwin, Schwartz, & Damri, 2017). Those who have more contact with others as well as have better social support show better cognitive functioning in later life. Moreover, those who experience more strain and conflict in their relationships show worse cognitive functioning (Liao et al., 2014; Tun, Miller-Martinez, Lachman, & Seeman, 2013). It is emotional not instrumental support that buffers cognitive decline (Ellwardt, Aartsen, Deeg, & Steverink, 2013), yet the mechanisms are still unclear. There is little known as to whether interventions to increase or improve social

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relationships would have benefits for cognitive aging. Arguably, the apparent benefits of social engagement may operate through (or in conjunction with) the increased cognitive activity (conversation, problem solving, collaboration) that typically accompanies social interaction.

There is also evidence that the relationship between social contact and memory is moderated by personality (Segel-Karpas & Lachman, 2016). Social contact had more beneficial effects for those high on extraversion than for those who were less extraverted. In contrast, those who were high in neuroticism showed less cognitive benefit from social interaction than those who were less neurotic.

Attitudes and Beliefs

The beliefs one holds about aging make a difference for cognitive performance. Research by Becca Levy and colleagues (Levy, Zonderman, Slade, & Ferrucci, 2011) found that those who hold negative stereotypes about aging in early life are more likely to show declines many years later. There is also evidence that stereotype threat plays a role in cognitive performance (Hess, Auman, Colcombe, Rahhal, 2003). There is a widespread stereotype that memory declines with age and that older adults have worse memory than younger adults. Under threat conditions, that is when this stereotype is invoked, older adults perform worse than when they are under non-stereotype conditions (Barber, 2017).

Another important set of beliefs is tied to self-efficacy (Bandura, 1997) and sense of control (Lachman, Neupert, & Agrigoroaei, 2011). Expectancies that one can be successful on a task or that one has the abilities to do well make a difference for outcomes. Those who believe they are in control of outcomes such as cognitive performance show better performance. Moreover, control beliefs are predictive of the course of cognitive change in later life.

Older adults are more likely than younger adults to rate their memory as poor, that is they have lower memory self-efficacy (Hertzog, Dixon, & Hultsch, 1990) and they are more likely to believe that they do not have control over their memory (Lachman, 2006). Such beliefs are a risk factor for poor memory and for accelerated memory declines (Windsor & Anstey, 2008). Indeed, those with lower control beliefs are less likely to use adaptive strategies for cognitive challenges (Lachman & Andreoletti, 2006). Those who have higher control beliefs improve more on cognitive tests with practice and are less likely to show aging-related declines in cognitive functioning (Caplan & Schooler, 2003). Most cognitive training studies do not include a focus on expectancies and beliefs. Unfortunately, if beliefs are not directly targeted, they are not likely

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to change even if performance does improve (Parisi, Gross, Marsiske, Willis, & Rebok, 2017; Lachman & Leff, 1989). Thus, there is a need to directly address beliefs in cognitive interventions to increase the benefits. Addressing the negative stereotypes and low expectancies for cognitive aging can result in increases in persistence and effort in using adaptive strategies in the face of declining abilities.

Subjective age is another construct related to cognitive aging. On average the older one is the greater the discrepancy between one's chronological age and how old they feel. Those who feel younger to a greater extent have better health and cognitive performance (Stephan et al., 2014). Moreover, an older subjective age was associated with a higher likelihood of cognitive impairment and dementia, and this association was partially due to physical inactivity and depressive symptoms (Stephan et al., 2017). There is also support for the alternative view that cognitive performance has an impact on subjective age in that if one experiences poor cognitive functioning relative to others one's age, it can lead to an older subjective age (Hughes & Lachman, 2016).

Moderating Variables

Several variables (some qualitative in nature) are thought to play a role in moderating the strength or direction of associations between specific risk factors and cognitive performance or change in aging. Prominent among these moderator variables are education, race, SES, age sex, and personality. If associations are specific to (for example) males but not females, then it implies that sex-specific mechanisms may be operating—and that sex-specific interventions may be required. Failing to investigate such moderators may lead to imprecision in results. In this section we briefly review three such moderators, education, race, and personality. Because of their centrality to brain and cognitive aging, we discuss two other moderators, age and sex, in more detail in a later section.

Education. Educational attainment is strongly related to level of cognitive functioning throughout adulthood. In fact, Langa and colleagues found that the decreased prevalence in dementia in the U.S. from 2000 to 2012 was largely attributed to increases in educational attainment. Yet, it is not clear whether education is also related to differential changes in cognition. A 12-year longitudinal study showed that higher education was associated with better cognitive performance but not with slowing of decline (Zahodne et al., 2011). Similar results were found in the Midlife in the United States (MIDUS study) over a 9-year period (Hughes et

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al, 2018). However, in some cases those with higher education have been found to maintain their functioning longer, and in other cases there are no differences in the onset of cognitive declines as a function of education. Moreover, in some studies, those with higher education have shown delays in declines and steeper slopes of decline than those with less education (Stern, 2012; Zahodne, Sol, & Kraal, 2017). This finding has been linked to the cognitive reserve hypothesis (Stern, 2009) which suggests that those with higher education have more reserve capacity and thus can delay functional declines associated with underlying pathology longer than those with less education. Other aspects of socioeconomic status are also related to cognitive functioning, such as childhood adversity, often operationalized as level of parents' education or degree of financial difficulties in childhood (Richards & Wadsworth, 2004).

Most often education is completed in early adulthood and the focus is on its long-term effects. These effects may be cumulative and indirect in that those with more education are more likely to engage in adaptive and healthy behaviors such as physical exercise, healthy diet, or cognitively stimulating activities. This raises possibilities for interventions that target those who are most vulnerable, i.e., those with lower education levels. In the MIDUS study, Lachman, Agrigoroaei, Murphy, & Tun (2010) found that those with low educational levels who engaged in more frequent cognitively stimulating activities, comparable to those with higher education, had memory performance that was similar to their higher education counterparts. This suggests that there are ways to compensate for lower SES or less education by engaging in lifestyle behaviors that are more consistent with those with more education. Another question of interest is whether obtaining education in middle age or later life would yield similar benefits to those seen with typical education in early adulthood. There is much interest in lifelong learning and adult education and retraining in the workforce. Little is known, however, if the advantages of education obtained later in life will parallel what is found for early life education. To some extent education is a form of cognitive stimulation and activity. Thus, it is plausible to assume that benefits for cognitive aging will be found no matter when education is obtained.

Race. Although studies show race differences in cognitive performance, these have been largely attributed to differential educational and occupational experiences and differences in environmental exposures (Glymour & Manly, 2008). Moreover, to date there is little evidence for race differences in the trajectories of cognitive aging. Changes in cognition over time seem to follow a similar course for African Americans (AA) and Caucasians (Manly, Jacobs, Touradji, &

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Small, 2002), although recent evidence indicate that there may be racial differences in predictors of cognitive impairment (Kaup et al., 2015). AA have a higher incidence of AD, but there is little understanding as to why this is the case, although there appear to be potential racial differences in vulnerability to genetic risk factors (Murrell et al., 2006). It is possible that differential health effects (e.g. higher levels of diabetes or heart disease among AA) or environmental differences (pollutants, stressors) could help to explain this (Ighodaro et al., 2017). Contextual factors such as segregation, educational resources, and discrimination have been found to contribute to race differences in cognition and cognitive decline (Glymour & Manly, 2008; Zahodne, et al., 2017).

Personality. Personality traits have been examined in relation to cognitive aging. There are consistent relationships such that those who have higher neuroticism show lower cognitive functioning, and those who are more conscientious and more open to experience have better cognitive functioning (Graham & Lachman, 2014). The relationships between personality and cognition vary by age, and those who have a more stable personality show better cognitive functioning (Graham & Lachman, 2012). What still is unknown is to what extent personality can serve a protective function. There is some suggestion that those who are higher in neuroticism are more likely to develop AD and those who are more conscientious are less likely to develop AD (Johannsson et al., 2014; Terracciano et al., 2014). Personality also is related to resilience in the face of AD pathology. Those with more adaptive personality profiles (ie. low neuroticism or high conscientiousness) were less likely to show symptoms of AD even with underlying AD neuropathology; and those with high neuroticism or low conscientiousness were less likely to remain asymptomatic. Recent findings suggest that personality change is related to dementia (Terracciano et al., 2017), in that those who have cognitive impairment show less stability of personality traits than those who are of comparable age without evidence of dementia.

II. Interactions among Risk and Protective Factors

Multicomponent Observational and Intervention Approaches

Most research on protective factors for cognitive declines has focused on single factors and their relationship with cognitive health. Another promising approach is to examine multiple factors in concert, as they exist in vivo. We know that physical activity and social activity are both good for cognitive health, but we know little about how these work together. There is

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interest in learning more specific information about the recommended dosage and most effective combinations of different protective factors.

Agrigoroaei and Lachman (2011) examined the cumulative contribution of psychosocial and behavioral protective factors (i.e., control beliefs, quality of social support, and physical exercise) to cognitive functioning and decline across ten years in the MIDUS study. They found that the more protective factors the better the cognitive performance, over and above well-established correlates and risk factors such as functional health, smoking, drug and alcohol use, and engagement in cognitive activities. The particular combination did not matter in that any two of these factors was better than any one factor. Moreover, the episodic memory scores among people with lower education, who engaged in more protective behaviors, were comparable to those of respondents with higher education. Participants with a greater number of protective factors showed lesser decline in reasoning over a ten-year period, especially for those with lower education. These results suggest that educational differences in cognitive performance and change can be attenuated by modifiable psychosocial and behavioral protective factors. Furthermore, this suggests that interventions that are multimodal may be more effective than those that target just one factor.

A 2-year multidomain intervention that included diet, exercise, cognitive training, and vascular risk monitoring with an at-risk group of older adults in Finland found positive results for maintenance of cognitive functioning (the FINGER study; Ngandu et al., 2015). However, some (e.g., Kraft, 2012) have argued that there is not enough evidence to conclude that multimodal interventions are more effective than individual interventions targeting cognitive or physical activity. Much research is examining directly whether combined training (e.g., both physical exercise and cognitive training) is more effective than targeting one component (Livingston et al., 2017). A noteworthy example is the Multidomain Intervention on Cognitive Function in Elderly Adults With Memory Complaints (MAPT) study (Vellas et al., 2014), which examined the contribution of multiple components, omega-3 supplementation alone, multidomain intervention alone (consisting of nutritional counseling, physical exercise, cognitive stimulation), omega-3 plus multidomain intervention, or a placebo on cognitive decline. Like many such studies (Ngandu et al., 2015), the early MAPT results were somewhat mixed (Andrieu et al., 2017). Another example is the INSIGHT Study, a 4-month randomized controlled trial in which healthy adults ages 18-43 were enrolled in one of four conditions: (1)

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fitness training; (2) fitness training and computer-based cognitive training; (3) fitness, cognitive training, and mindfulness meditation; or (4) active control (Daugherty et al., 2018). Whereas the combination of fitness and cognitive training produced gains in visuospatial reasoning that were greater than in the active control, this was not the case for other cognitive tasks. The effectiveness of the various combinations of training varied across cognitive outcome measures.

The Experience Corps (Fried et al., 2004; 2013) in which older adults volunteered in Baltimore inner city schools to tutor elementary school children found evidence for positive changes in the brain involving increases in hippocampal and cortical volume (Carlson et al., 2015). The positive changes may be attributed to the multimodal nature of the intervention, which included increased physical activity, cognitive stimulation, and social interactions.

A 25% reduction in seven modifiable risk factors including diabetes, hypertension, obesity, depression, physical inactivity, smoking, and education/cognitive inactivity could prevent up to 3 million cases of ADRD worldwide and 492,000 cases in the United States (Yaffe et al., 2014). Given the knowledge we now have regarding modifiable factors that can slow, reduce or even reverse cognitive declines or reduce the risk of dementia, there is a need to ensure that adults engage in these adaptive behaviors. Thus, there is renewed interest in developing effective behavior change programs to promote a healthy lifestyle that supports good cognitive health. This would involve a focus on behavior changes such as regular exercise, better sleep, improved diet, social interaction, and cognitive stimulation. Interventions can be useful not only for changing behaviors but also for identifying the mechanisms that link cognitive aging with lifestyle factors. Further research is needed to indicate when and how often to intervene. A promising direction for cognitive interventions is to examine if earlier timing is better and to what extent booster sessions are necessary.

III. Role of Non-Modifiable Risk and Protective Factors

Whereas the previous sections reviewed new approaches and recent information on modifiable risk and protective factors, as they influence and differentiate trajectories of normal cognitive aging, in this section we attend to the main clusters of relatively non-modifiable risk factors and biomarkers and how they might moderate the influence of other more malleable factors. The effects of non-modifiable factors can occur in the form of direct associations, but also in more complex configurations, such as interactions, panels, risk indexes, and networks. Indeed, they may combine with modifiable factors, even in the direction of cognitive

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maintenance and positive outcomes. Thus, these non-modifiable factors serve an important function in identifying risks that may lead to preventive interventions. We provide a brief overview of genetic risk for cognitive decline and dementia, as conveyed by polymorphisms identified in genome wide association studies (GWAS) for their role in Alzheimer's disease (AD) risk (especially Apolipoprotein E (*APOE*)) or cognitive aging risk (e.g., Brain derived neurotrophic factor (*BDNF*)). Next we describe the roles that chronological age and sex can play in moderating observed associations between genetic and other biomarkers, on the one hand, and cognitive trajectories and statuses, on the other hand. Stratification by age or sex can reveal differences in associations and mechanisms, including functions such as magnification of severity and precision of mechanistic pathways. Accordingly, we review new approaches, based on trajectory analyses, to detecting and characterizing subsets of aging adults who have high risk profiles (e.g., for AD) and yet show minimal signs of exacerbated cognitive decline.

Furthermore, we review briefly new and objective approaches to identifying subsets of aging adults who demonstrate either superior levels or sustained trajectories of cognitive performance, thus qualifying as “successful” or “exceptional” cognitive agers. For both resilient and exceptional cognitive aging adults, the key effort is in phenotyping them—finding the combinations of protective or risk-reducing factors that promote such healthy brain and cognitive aging. A theme running throughout this section is that of advancing precision assessment and personalized and targeted interventions in the period of brain and cognitive aging prior to an AD diagnosis.

Genetic Risk

Estimates from prominent behavioral genetic (twin) studies of the heritability of general intelligence (or “g”) are typically high, including 60-80% for standard intelligence test performance (Harris & Deary, 2011; Kremen et al., 2016). This suggests that unmodifiable factors (in general) play a substantial role in influencing individual differences in overall cognitive ability in older adults. However, three qualifications relevant to the present review have emerged. The first qualification is that there is indeed considerable room for the influence of other risk factors, some of which may be modifiable, and these may represent aspects of the environment, including risk exposures. The second qualification is that calculations of heritability of cognition are generally less dramatic when the phenotype is not performance level but cognitive change in specific domains (Harris & Deary, 2011; Reynolds & Finkel, 2015;

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Tucker-Drob et al., 2014). Trajectories are a crucial target for cognitive aging research. A third qualification is that examination of individual risk genes and their differential associations with specific domains of cognitive level and change may reveal useful information about underlying mechanisms related to subsets (e.g., carriers/non-carriers, normal/impaired, female/male) of aging individuals. Therefore, a key issue for the present review of research on normal cognitive aging is what genotypic influences affect what cognitive functions (and trajectories) in the context of what underlying mechanisms?

Three reasonable points of origin from which to investigate these connections are (a) a small cluster of genotypes that have been extensively explored for their independent associations with cognitive performance and change in non-demented and non-impaired older adults, (b) *Apolipoprotein E (APOE)*, the most prominent genetic risk factor for AD, and (c) other AD risk genotypes discovered in genome wide association studies (GWAS). Note that for (b) and (c), we refer to genetic risk for late-onset or sporadic AD, the most prevalent neurodegenerative disease, and known to be multi-factorial in origin. We do not cover the other form of AD, the rare (about 5% of AD cases) early onset or familial AD (EOAD), for which symptoms typically appear in the 40s and 50s. The incidence of EOAD is determined by inherited mutations in three genes (*Presenilin 1*, *Presenilin 2*, and *Amyloid Precursor Protein*) controlling corresponding proteins that are associated with beta amyloid deposition (i.e., plaques) in the brain. In contrast to the genetic determinism of EOAD, the genetic predictors of sporadic AD are probabilistic, likely combining with other risk factors to produce the neurodegeneration typical of transitions from normal to impaired aging and dementia (Fotuhi et al., 2009). The argument for including AD genetic risk factors in studies on non-demented cognitive aging is that preclinical period of neurodegenerative changes associated with emerging AD can reach back more than a decade prior to diagnosis. Therefore, AD genetic risk factors may exert their influence on cognitive decline—and especially accelerations in cognitive decline associated with mild cognitive impairment—during a period that appears to be asymptomatic, seemingly normal cognitive aging.

Numerous studies have explored genetic approaches and specific genotypes for their associations with a variety of cognitive phenotypes of normal aging. Several in-depth reviews locate this research direction in its biological, methodological, and theoretical context (e.g., Harris & Deary, 2011; Kremen, Panizzon, & Cannon, 2016; Papenberg et al., 2015). An early

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approach employed “candidate genes” to explore associations with cognitive phenotypes potentially linked to underlying mechanistic operations in identified regions of the aging brain. Among the prominently—and most successfully—investigated candidate genes for normal cognitive aging have been brain-derived neurotrophic factor (*BDNF*) and catechol-O-methyl transferase (*COMT*). Because these genes have been linked to functioning within the hippocampus and prefrontal cortex, respectively, they have been investigated with performance on episodic memory and executive function tasks. Although widely investigated in these and other neurocognitive aging contexts, these two candidate genes have produced selectively significant results but inconsistent patterns overall (e.g., Barnett et al., 2008; Mandelman & Grigorenko, 2012). Much more promising has been recent work investigating these two polymorphisms in various combinations (panels, risk scores) or interactions (gene x gene; gene x environment; gene x health) and with specialized outcome measures evaluated longitudinally (e.g., Das et al., 2014; Erickson et al., 2009; Raz et al., 2009; Sapkota et al., 2017). Notably, this progress fits with the direction of the present review, in which interactions of modifiable and non-modifiable risk factors are of direct interest.

Apolipoprotein E (*APOE*) is the most prominent and commonly studied genetic risk factor for AD. Differentiated by three isoforms, carriers of the $\epsilon 4$ allele (especially homozygotes) are at elevated risk of developing AD, whereas carriers of the $\epsilon 3$ (AD neutral) and $\epsilon 2$ (potentially protective) are at relatively low risk (Liu et al., 2013; Wisdom et al., 2011). The key question for this review is whether *APOE* $\epsilon 4$ carriers are also at risk for preclinical impairment and exacerbated but non-impaired normal cognitive decline. Regarding mild cognitive impairment (MCI), several studies have implicated the predictive role of the $\epsilon 4$ (e.g., Brainerd et al., 2011; Dixon et al., 2014), with the latter study reporting the intriguing result that *COMT* contributed complementary prediction patterns to *APOE*. An early meta-analysis provided an initial assessment of the role that *APOE* might play in predicting cognitive performance in non-demented older adults (Small et al., 2004). Since that time, much more research has been reported showing increasingly interpretable patterns of influence, although especially in combinations with other AD genetic risk factors (e.g., Andrews et al., 2017), normal cognitive decline risk genes (Sapkota et al., 2015), as well as with modifiable cognitive aging risk factors (e.g., McFall et al., 2015; McFall et al., 2016; Raz et al., 2009). In an investigation of conversion

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from mild cognitive impairment (MCI) to AD, it was the absence of *APOE* $\epsilon 4$ alleles that best predicted the stability of MCI over a three year period (Clem et al., 2017).

In addition to *APOE*, GWAS have identified 20 genetic loci that are associated with AD (Andrews et al., 2017). Although none of these variants bear the function load of *APOE*, some may serve purposes useful to the current review. Specifically, these lesser known AD variants may (a) mark coordinated pathophysiological mechanisms of AD, (b) contribute to predictive panels or polygenic risk scores, (c) be applicable in to-be-determined combinations in predicting exacerbated or impaired cognitive decline (or AD progression), or (d) contribute to *APOE*-based panels that interact with modifiable risk factors in predicting cognitive change (e.g., Carrasquillo et al., 2015; Darst et al., 2017; Zhang & Pierce, 2014; Sapkota et al., 2017). Polygenic risk scores are panels of multiple risk variants with relatively small direct effects on the phenotype of interest, but which may combine to represent coordinated pathways within networks of neurobiological influence. These networks may also include other biomarkers or risk factors (Gaiteri et al., 2016) and such networks may vary by age (e.g., magnification among older adults; Papenberg et al., 2015) or sex (McDermott et al., 2017; differential for females and males). Recently, such genetic networks have included sets of risk genes for both normal cognitive aging and AD (Sapkota & Dixon, 2018) in predicting non-demented cognitive trajectories.

In sum, an important point is that in predicting cognitive change, impairment, and dementia, genetic risk interacts with other potentially modifiable risk conferred by a variety of factors of everyday life (activities, exercise, health). Moreover, as we will see in the next subsections, these dynamic associations may also be moderated by age, sex, and even *APOE* $\epsilon 4$ status. Therefore, risk and protective factors may be part of the network of predictors that apply differentially within certain categories of aging demographics.

Age and Sex: Not Just Difference Makers but Tools of Precision Research?

The aptly named “triad” of risk for sporadic AD includes three major elements: Chronological age (older is worse), sex (female is worse), and *APOE* (worse for $\epsilon 4$ carriers) (Riedel, Thompson, & Brinton, 2016). The simplicity of these three major AD risk factors is remarkable, given all the effort expended on discovering hallmarks and biomarkers of AD through invasive or complex procedures such as PET scans (for amyloid burden), GWAS (for additional AD-related genotypes), lumbar punctures (for CSF assays of beta amyloid and phosphorylated tau), brain tissue analyses (for confirmation of AD diagnosis and biomarker

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analyses), and blood-based biomarker assays (including omics-based unbiased discovery analyses). They are straightforward to measure with accuracy, available as variables in many research studies and data archives, and typically reported at least in background or demographic tables or included as covariates. However, some differences in how these variables are used and interpreted are apparent. We focus on using age and sex advantageously in research on cognitive aging.

Using Age Advantageously. A first question from some observers might be, *Why use age at all (or at most as an index)?* For other observers, a contrary question might be, *What is wrong with using age (e.g., to form groups for comparison)?* We will not reprise the decades-long discussions of the status of chronological age in aging research (see Baltes & Willis, 1977; Birren & Cunningham, 1985; Dixon, 2011). Three key points have been enumerated frequently and persuasively: (a) age may be useful as an index or metric of aging but it is not a cause or source of theoretical explanations; (b) age is a prominent but not the only way to display time-related trajectories in cognitive aging (e.g., biological age, functional age); and (c) cross-sectional comparisons reveal potentially promising age or group differences in performance and in predictor-performance associations but their viability as representations of actual change or platforms for testing mechanistic hypotheses cannot not be verified and might be considered skeptically under most prevailing assumptions (Baltes, 1968; Baltes, Lindenberger, & Staudinger, 2006; Schaie, 1965; Schaie 2012).

Nevertheless, it is true that age per se is the single most predictive biomarker of sporadic AD, and thus it should be useful in some settings and for some purposes. Three such examples of the usefulness of age are relevant in this review. First, a growing number of recently published papers on actual cognitive trajectories (as often displayed in spaghetti plots) reveal the rich variability and differentiation of age changes for many cognitive functions (Dixon et al., 2014; Josefsson et al., 2012). When analyzed appropriately such trajectories can produce meaningful representations of overall function of cognitive change across a given band of age (Galbraith, Bowden, & Mander, 2014). With (a) relatively large data sets, (b) a broad band of age, (c) well-measured (and even latent) cognitive variables, and (d) application of increasingly available statistical packages for change analyses, these data can highlight the general aging trend but also the vast individual differences in level, slope, and variability of change patterns. Such analyses have the additional advantage of including age directly. Second, contemporary statistical

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techniques (e.g., parallel process models in latent growth curve analyses) permit the incorporation of theoretically relevant predictor variables in trajectory analyses. These can include non-modifiable predictors (genotype), modifiable but not changing predictors (baseline education), and modifiable predictors that may change over time (lifestyle or health risk factors) (McFall et al., 2016; Sapkota et al., 2017). Moreover, analyses can accommodate single candidate predictors as well as a variety of predictor interactions (e.g., Thibeu et al., 2017). Third, given the often-observed heterogeneity of age-related levels of performance (even within older adults) and the intriguing findings of age-related changes in predictor patterns, it is possible to use a reasonable break point of age (in a broad age band sample) to stratify and conduct these analyses separately for two or more age groups. Using similar procedures, researchers have advanced the hypotheses that some biomarkers, including genetic polymorphisms, may have magnified effects for very old, as compared with young-old, adults (Lindenberger et al., 2008; Papenberg et al., 2015).

In sum, age is a major risk factor for AD and cognitive decline but should be used carefully in research. All longitudinal data are, at heart, age-based, but using it as a metric of change, with no assumptions about alleged causal roles, permits analytical and interpretive advantages. As such, age is not just a variable associated with performance differences, but it is also a variable that can provide opportunities for testing mechanistic hypotheses, developing individualized clusters, and leading to precision interventions. This is especially the case given that trajectory groups may demonstrate different patterns of predictions by biomarker and risk or protective factors (McFall et al., 2015; Zahodne, et al., 2016). Moreover, the onset and slope of declines varies across persons and cognitive dimensions.

Using Sex/Gender Advantageously. We adopt a standard definition of these two terms, but recognize that there are areas of grey (non-binary, inexact separation, and exceptions) between them. Accordingly, in this discussion sex refers to biological and physiological differences in function or mechanisms between males and females and gender refers to differences related to socialization or culture, including associated characteristics, exposures, roles, and identity for women and men. Both sex and gender are of interest in the wider range of brain and cognitive aging, but for present purposes sex and sex-related phenomena are emphasized. Sex differences—and, more importantly, sex-related mechanisms—are of increasing importance in the study of brain and cognitive changes associated with decline,

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dementia, and mechanisms thereof. The National Institutes of Health has adopted a stringent policy to enhance research on sex as a biological variable. When integrated into research designs, it is possible to examine differences in a variety of areas, including brain and cognitive aging research, as well as research on neurodegenerative diseases (Tierney, Curtis, Chdertkow, & Rylett, 2017). One goal is to provide more complete data sets (in terms of sex representation), more generalizable results (to both sexes) and deeper analyses of the biological mechanisms underlying such observations as sex differences in cognitive performance, AD incidence and prevalence, and response to medications (including molecules in AD intervention research). Recently, new and large-scale research programs (e.g., Canadian Consortium on Neurodegeneration in Aging; U.S. National Institute on Aging Research Programs on Alzheimer's Disease and Related Dementias) have emphasized, and in some cases compelled, the investigation of sex and/or gender differences in basic, clinical, and intervention research.

Thus, the advantageous use of sex and gender in research covered in the present review is predominantly to further investigate sex differences in cognitive performance and change, mechanisms underlying those differences, and how they have differential implications for longer term trajectories and clinical outcomes. For example, among the replicated results pertaining to sex effects in non-demented older adult cognitive performance is the difference in mean performance levels (Herlitz & Rehnman, 2008; Jack et al., 2015; Weber et al., 2014). Close inspection usually reveals that these differences are relatively small (in magnitude) and the female-male distributions display considerable overlap. However, they may conceal some important and emerging differences, as females may also undergo earlier pathogenic brain changes and steeper declines in performance (Zhao, Mao, Woody, & Brinton, 2016). Moreover, recent research has indicated that female carriers of the *APOE* $\epsilon 4$ risk allele may experience differentially higher risk for AD than do their male counterparts (Altmann, Tian, Henderson, & Grecius, 2014). This and other sex-related neurobiological factors may play a role in the reported greater prevalence of AD for females than males. Moreover, it may indicate the importance of stratifying for sex when AD genetic risk is considered. In sum, an advantageous use of sex as a biological variable includes the possibility of examining many mechanistic analyses separately for males and females. It may also indicate that the importance of including both sexes in AD-related intervention trials should consider the possibility of powering the study so that

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differential factors and responses can be assessed. We present an example of this in the next subsection.

IV. Risk and Protective Factors: Alternative Pathways to Cognitive Health

Cognitive Reserve and Resilience to Risk

A pleasantly perplexing issue in the field of brain and cognitive aging is that some older adults seem to retain adaptive, if not relatively high, levels of cognitive performance, despite (a) advancing age, (b) elevated genetic or familial risk for AD, and (c) actual observed AD neuropathology (amyloid deposition). The conceptual framework of reserve has been postulated to account for such intriguing discrepancies in susceptibility to normal or pathological brain changes with aging (Stern, 2002, 2012). Abundantly researched and evaluated, reserve has been differentiated into complementary brain (relatively passive) and cognitive (relatively active) components. The concept of brain reserve reflects the contention that individual differences in neural structure, including ongoing neurodegenerative processes associated with impairment and AD, lead to differences in pathological burden and vulnerability to early or exacerbated cognitive decline. The concept of cognitive reserve refers to a body of epidemiological, neuropsychological, and biomarker evidence that lifelong activities summarized by extent of education, lifestyle engagement, and occupational complexity are associated with sustained cognitive adaptation (Cabeza et al., 2018; Marioni et al., 2012; Stern, 2009, 2012). Reserve has an established position in the lexicon of research and theory in normal cognitive aging, as well as preclinical transitions to AD (Arenaza-Urquijo et al., 2015) and other neurodegenerative diseases (Borroni et al., 2012). Much progress in identifying neuroimaging and lifestyle factors indicative of reserve has been made (e.g., Jones et al., 2011; van Loenhoud et al., 2017). Recent approaches integrate neuroimaging markers with genetic or cognitive markers to capture a flexible and promising model of cognitive reserve (e.g., Ferrari et al., 2013; van Loenhoud et al., 2017).

Although reserve has proven to be a fertile conceptual framework addressed to a salient issue in brain and cognitive aging, as a scientific concept it is still hypothetical and its main explanatory devices are only indirectly indicative of its operation. In principle, a full examination of reserve might benefit from (a) direct measures of the dynamics of vulnerability (or risk), (b) the presence of countervailing buffers or protection, and (c) evidence of sustained levels and slopes of cognitive performance beyond that expected for individuals with elevated risk but

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reduced protection. To be sure, pieces of this dynamic model have been observed. Moreover, that the indirect measures of reserve—e.g., higher cumulative levels of life experiences that are cognitive-intensive (education, job complexity)—are associated with cognitive health and dementia delay are suggestive. The process of compensation refers to the recruitment of neural or behavioral resources to address limitations due to cognitive and brain aging especially in high demand situations (Bäckman & Dixon, 1992; Cabeza et al., 2018; Dixon, Garrett, & Bäckman, 2008). It is likely that the balance between available cognitive reserve and prevailing cognitive deficits (in the context of environmental demands) may determine the extent to which compensatory mechanisms may be recruited and deployed (Dixon & de Frias, 2007; Reuter-Lorenz & Cappell, 2008). The processes per se of reserve and the mechanisms underlying the concept and its effects on cognition may be identifiable and quantifiable. To this extent, specific experiences may be operationally defined, tested experimentally or in interventions, and evaluated for their promise in promoting reserve and healthier brain aging in mid-life and beyond.

One corollary concept fulfilling some of these criteria has emerged: This is the concept of cognitive resilience. A consensus definition refers to actual cognitive maintenance (over time) despite objective evidence for AD risk, such as being a carrier of the $\epsilon 4$ allele of *APOE* (Kaup et al., 2015). It is well-known that not all genetic risk carriers convert to clinical diagnosis of AD, and in fact some of them seem to maintain adaptive, if not high and sustained, levels of performance into late life (Ferrari et al., 2013). If substantial samples of individuals with this combination of characteristics—who are also participants in larger-scale longitudinal studies—could be detected and assembled, the process of resilience could be testable. In addition, some studies would likely have variables representing potential risk of protection factors that may be contributing to the emergence of resilience in this subpopulation. A reasonable pool of such potential mechanistic markers of resilience would include both modifiable and non-modifiable risk and protective for cognitive decline and dementia.

Recently, Kaup and colleagues (2015) used longitudinal data from Health ABC Study to examine slope deviations of genetic risk carriers, as compared with the remainder of the sample, and classified cognitively resilient individuals as those who were *APOE* $\epsilon 4$ carriers and displayed relatively high cognitive change slopes. Importantly, after classifying a substantial resilient group, the researchers conducted prediction analyses as stratified by race. Different patterns of

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predictors were observed for white and black carriers. Using a similar approach and data from the Victoria Longitudinal Study, McDermott and colleagues (2017) focused on episodic memory performance (represented in a latent variable), as memory decline is a cardinal early marker of preclinical AD. The trajectory analyses set the algorithm for comparing both level and slope as determinants of classification for *APOE* $\epsilon 4$ carriers. Their sample lacked racial diversity, but they stratified by sex, reasoning that males and females often perform differently on memory (Herlitz & Rehnman, 2008) and females have higher AD prevalence than males. Their results showed that risk and protective predictors of resilience differed by sex, with more modifiable predictors detected for females. These results were largely replicated for resilience as defined by another AD risk gene, Clusterin (*CLU*).

In sum, cognitive reserve and resilience are differentiable conceptually and methodologically but sponsor complementary research goals and activities. Both deserve further attention and perhaps a merging of techniques and issues. Resilience studies feature objective criteria based on dynamic data and sophisticated statistical analyses for classification. Such studies are also amenable to stratification for key group comparisons of predictor patterns. Observing similar phenomenon but different predictors by racial and sex status holds great promise for future mechanistic analyses and precision intervention to promote healthier (resilience) cognitive functioning, even for individuals with substantial and readily measurable AD risk.

Alternative Pathways: A Continuum of Trajectories and Outcomes of Cognitive Aging

How can a continuum of cognitive concepts and phenotypes, including reserve, resilience, normal aging, and exceptional (or “successful”) aging, be theoretically differentiated and empirically classified? One way to begin addressing this challenge is presented in the model presented in Figure 2. This figure (based on Dixon, McFall, & McDermott, 2017) shows a flowchart with one common input (normal cognitive aging), two generic mechanisms (AD biomarker risk, brain aging vulnerability risk/protection), and four provisionally distinguishable pathways and clinical outcomes of aging. The model provides a template for discriminating these pathways (column 2)—theoretically and empirically—as the lead from normal cognitive aging (column 1) to four alternative trajectory patterns or clinical statuses (column 3). A brief interpretation of each pathway and outcome is provided in column 4.

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The top pathway (row 1) is the one that is likely for many middle-aged and aging adults, at least until they accumulate additional risk in advancing age. Low AD genetic risk would be expected given that the predominant genotypes of *APOE* include (delineated as *APOE* $\epsilon 4$ -, including the most common $\epsilon 3/\epsilon 3$ configuration). Nothing conveys immunity to cognitive impairment and dementia, so this group, without further phenotyping, would be expected to follow multiple trajectories leading to multiple potential outcomes. The second row pertains to individuals who have high genetic risk but normal risk reduction from other factors. Initially expected to be in the normal range of cognitive performance (level and slope), these individuals are at elevated risk for early cognitive decline, transitions into cognitive impairment, and eventually AD. For these individuals, early detection and implementation of modifiable risk reduction interventions may lead to delayed impairment, if not prevention (Anstey et al., 2014).

The third row pertains to the pathway to resilience, as described above. In this pathway, high AD risk is counter-balanced by elevated risk reduction or protective factors with the ensuing range of trajectories encompassing normal to sustained levels and slopes. If resilience is classified, the predictors (reflecting mechanisms) can be identified and targeted in precision interventions. The interventions may be applied to in order to extend the period of resilience, but also potentially to initiate resilience in the previous pathways. Finally, the fourth pathway is one of long-term interest in a variety of fields of aging (Pruchno, 2015). It depicts a potential pathway whereby brain and cognitive exceptionality may be attained and maintained by select individuals. Often referred to as successful cognitive aging (Depp & Jeste, 2006) or superaging (Rogalski et al., 2013), such an outcome could be promoted by the propitious combination of low AD genetic risk and elevated protective or risk-reducing factors. Again, the research agenda would include determining the phenotype of exceptional brain and cognitive aging, and then examining the predictors, both modifiable and non-modifiable. For those fortunate enough to be following this aging pathway, interventions might still be useful for managing protection, and perhaps sustaining or enhancing it with advancing age. For those following other aging trajectories, it is possible that the modifiable predictors of exceptional brain and cognitive aging could be useful in a risk-reducing capacity in middle- to late-life.

We emphasize that the model is designed to represent common clusters of pathways and conditions but is broad enough to accommodate many intermediate and changing circumstances. We also note that the outcome trajectories and statuses can be discriminated conceptually and

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sometimes empirically but that they comprise areas on a continuum of brain and cognitive aging. We note that the model represents the pathways as influenced by genetic and modifiable risk factors, such as those described above, but implies that they may interact in intensify risk or magnify risk reduction. Not specifically included in the model is the fact that some of these mechanisms may vary by important variables of stratification, including sex, race, age, or APOE status. To examine these pathways, large-scale and multi-faceted longitudinal data would be required. To determine underlying mechanisms, experimental work will be useful. To explore interventions for personalized risk reduction or protection enhancement, prevention studies, including multi-factorial randomized control trials, are the method of choice (e.g., Anstey et al. 2014; Anstey et al., 2015; Barnes et al., 2015; Carlson et al., 2015; Ngandu et al., 2015). With these comparative pathways in mind, we turn now to the fourth scenario, that leading to exceptional brain and cognitive aging.

Cognitive Exceptionality: Risk Reduction and Protection Enhancement?

The vast individualized variability of non-demented aging cognitive trajectories is of increasing interest by researchers in both normal aging and AD. For both groups this diversity of change patterns presents an understudied but promising context discovery and validation of risk-reducing and protection-enhancing factors in cognitive aging (Depp, Harmell, & Vahia, 2012; Gefen et al., 2014; Yaffe et al., 2009; Zahodne et al., 2016). Traditionally, both cognitive aging and AD researchers have emphasized descriptive and explanatory work on typical and exacerbated decline, impairment, and transitions to AD. A complementary approach focuses on (a) establishing the validity of relatively “healthy”, “successful”, or “exceptional” phenotypes and (b) exploring their risk predictors in order to promote healthier brain aging through AD risk management, delay, or even prevention (Anstey, 2014; Barnes & Yaffe, 2011; Daffner, 2010; Dixon, 2010; Pruchno, 2015). Arguably, factors associated with sustained cognitive health may include those that are modifiable through early interventions, operating at a precision or even public health level.

A set of positive concepts of aging—typically known as “successful aging”—have circulated for several decades (Baltes & Baltes, 1990; Pruchno, 2015; Pruchno, Wilson-Genderson, Rose, & Cartwright, 2010; Rowe & Kahn, 1997) and recently benefited from critical reviews (Cosco, Prina, Perales, Stephan, & Brayne, 2014; Depp & Jeste, 2006). New conceptual and empirical applications to cognitive and brain aging have appeared (Depp et al., 2012; Fiocco

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& Yaffe, 2010) and focused on issues of objective and enriched classification, identification of associated risk and protective factors, and potential application to risk management and prevention. Successful efforts to characterize exceptional brain and cognitive aging have included a variety of methods: single-test averages, multi-test distributions, comparisons with younger adults, and, recently, trajectory analyses (Josefsson et al., 2012). Exceptional cognitive performance has been established for multiple domains of cognition including global cognition (Yaffe et al., 2009), executive function (de Frias & Dixon, 2014; de Frias, Dixon, & Strauss, 2009), and episodic memory (EM) (Barral et al., 2013; Dixon & de Frias, 2014; Harrison, Weintraub, Mesulam, & Rogalski, 2012; Josefsson et al., 2012).

Several programs of research have appeared. For example, the Northwestern SuperAging project defines “SuperAgers” as having EM performance similar to that of adults 20 years their junior. Benefits include maintained performance in other cognitive domains (Gefen et al., 2014) and fewer brain markers of AD pathology (Harrison et al., 2012; Rogalski et al., 2013). Complementary research from the Canadian-based Victoria Longitudinal Study (VLS) identified “cognitively elite” participants from a longitudinal panel as those individuals who scored above the (age x education) mean on a battery of 3-5 basic cognitive tasks. Whether applied to executive functioning (de Frias et al., 2009; de Frias & Dixon, 2014) or memory (Dixon et al., 2012; Dixon & de Frias, 2014; McFall et al. 2015), objectively classified cognitively-exceptional participants performed better on a variety of related tasks. The Swedish Betula Project used longitudinal memory trajectories to separate maintainers (i.e., moderate to high baseline EM score and better-than-average rate of change) from decliners and those with age-typical change (Josefsson et al., 2012). Being a maintainer was predicted by higher education, being female, living with someone, more physical activity, and being a Met carrier of the COMT gene. The trajectory approach has recently been applied to classification and determination of modifiable risk factor predictors (McDermott, McFall, & Dixon, 2017). The latter study stratified by age and found differing predictors for young-old and old-old groups.

In sum, objectively classifying exceptional cognitive aging can be accomplished with several methods. A key goal is to determine clusters of predictors, especially as they discriminate between exceptional groups and normal or declining groups. Such predictors may derive from multiple modalities (brain, genetic, lifestyle) and range in modifiability. Thus far, results indicate that strategies for promoting healthy brain aging may not be just the reverse of strategies for

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delaying decline or impairment. Precision approaches that target specific modifiable biomarkers may be useful in future intervention strategies to promote or sustain healthy brain and cognitive aging. Moreover, personalized interventions can target specific personal characteristics to maximize the likelihood of effective treatments.

V. Conclusion

As the world population continues to age and the prevalence of Alzheimer's Disease and Related Disorders is expected to rise, there is a concerted effort to identify early warning signs of accelerated cognitive decline, transitions to impairment, and impending dementia. There is evidence for wide individual differences in the nature of cognitive aging and these differences are reflected in variability in onset, level, and slope of trajectories (Dixon et al., 2014). Cognitive declines on some cognitive dimensions such as processing speed begin in early midlife for some adults (e.g., Hughes, Agrigoroaei, Jeon, Bruzzese, & Lachman, 2018). As reviewed in this chapter, researchers have identified multiple modalities of both modifiable and non-modifiable risk factors that hold promise for understanding how, why, and to what extent trajectories of cognitive change are predicted and differentiated with aging. Equally important to detect and catalogue are the risk-reducing or protective factors that predict favorable trajectories and outcomes, such as reserve, resilience, plasticity, and sustained exceptional cognitive performance. In this review, we emphasize the emerging importance of considering multi-modal dynamic and network approaches to examining interactions among common risk and protective factors. Such approaches may lead to better precision in both observational and intervention research. Although the ultimate goal is to prevent the onset of cognitive impairment and dementia, a more realistic aim, at least in the short term, may be to reduce or delay neurodegenerative risk and associated cognitive declines.

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References

- Agrigoroaei, S., & Lachman, M.E. (2011). Cognitive functioning in midlife and old age: Combined effects of psychosocial and behavioral factors. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 66B, i130-i140. doi: 10.1093/geronb/gbr017
- Agrigoroaei, S., Robinson, S. A., Hughes, M. L., Rickenbach, E. H., & Lachman, M. E. (2018) Cognition at midlife: Antecedents and consequences. Chapter 21. In C. D. Ryff & R. F. Krueger (Eds.), *Oxford Handbook of Integrated Health Science*: Oxford University Press.
- Altmann, A., Tian, L., Henderson, V.W., & Greicius, M.D. (2014). Sex modifies the APOE-related risk of developing Alzheimer's disease. *Annals of Neurology*, 75, 563–573. doi: 10.1002/ana.24135
- Alzheimer's Association (2016). Alzheimer's association report: 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 12 (4), 459-509.
- Andel, R., Kåreholt, I., Parker, M.G., Thorslund, M., & Gatz, M. (2007). Complexity of primary lifetime occupation and cognition in advanced old age. *Journal of Aging and Health*, 19, 397-415.
- Andel, R., Vigen, C., Mack, W.J., Clark, L.J., & Gatz, M. (2006). The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. *Journal of the International Neuropsychological Society*, 12, 147-152.
- Andrews, S.J., Das, D., Anstey, K.J., & Eastaer, S. (2017). Late Onset Alzheimer's disease risk variants in cognitive decline: The PATH Through Life Study. *Journal of Alzheimer's Disease*, 57, 423-436. <http://doi.org/10.3233/JAD-160774>
- Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., . . . & Vellas, B. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *The Lancet Neurology*, 16, 377-389. doi: 10.1016/S1474-4422(17)30040-6
- Anstey, K.J. (2014). Optimizing cognitive development over the life course and preventing cognitive decline: Introducing the Cognitive Health Environment Life Course Model

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- (CHELM). *International Journal of Behavioral Development*, 38, 1-10. doi: 10.1177/0165025413512255
- Anstey, K.J., Cherbuin, N., Herath, P.M., Qiu, C., Kuller, L.H., Lopez, O.L., ... Fratiglioni, L. (2014). A self-report risk index to predict occurrence of dementia in three independent cohorts of older adults: The ANU-ADRI. *PLoS ONE*, 9, e86141. doi: 10.1371/journal.pone.0086141
- Anstey, K.J., Eramudugolla, R., Hosking, D.E., Lautenschlager, N.T., & Dixon, R.A. (2015). Bridging the translation gap: From dementia risk assessment to advice on risk reduction. *The Journal of Prevention of Alzheimer's Disease*, 2, 189–198. doi: 10.14283/jpad.2015.75
- Arenaza-Urquijo, E.M., Wirth, M., & Chételat, G. (2015). Cognitive reserve and lifestyle: moving towards preclinical Alzheimer's disease. *Frontiers in Aging Neuroscience*, 7, 134. doi: 10.3389/fnagi.2015.00134
- Ashe, M.C., Miller, W C., Eng, J.J., & Noreau, L. (2009). Older adults, chronic disease and leisure-time physical activity. *Gerontology*, 55, 64-72. doi: 10.1159/000141518
- Bäckman, L., & Dixon, R. A. (1992). Psychological compensation: A theoretical framework. *Psychological Bulletin*, 112, 259-283.
- Ball, K.K., Beard, B.L., Roenker, D.L., Miller, R.L., & Griggs, D.S. (1988). Age and visual search: Expanding the useful field of view. *JOSA A*, 5, 2210-2219. doi: 10.1364/JOSAA.5.002210
- Baltes, P.B. (1968). Longitudinal and cross-sectional sequences in the study of age and generation effects. *Human Development*, 11, 145–171.
- Baltes, P.B., & Baltes, M.M. (1990). Psychological perspectives on successful aging: The model of selective optimization with compensation. In P.B. Baltes & M.M. Baltes (Eds.), *Successful aging: Perspectives from the behavioral sciences*. New York, NY: Cambridge University Press.
- Baltes, P.B., & Willis, S.L. (1977). Toward psychological theories of aging and development. In J. E. Birren & K.W. Schaie (Eds.), *The handbook of the psychology of aging* (pp. 128-154). New York, NY: Van Nostrand-Reinhold.

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Baltes, P.B., Lindenberger, U., & Staudinger, U.M. (2006). Life span theory in developmental psychology. In R.M. Lerner & W. Damon (Eds.), *Handbook of child psychology: Theoretical models of human development* (pp. 569-664). Hoboken, NJ: John Wiley.
- Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: Freeman.
- Barber, S., (2017). An examination of age-based stereotype threat about cognitive decline: Implications for stereotype threat research and theory development. *Perspectives on Psychological Science* 12, 62-90.
- Barnes, D. E., Mehling, W., Wu, E., Beristianos, M., Yaffe, K., Skultety, K., & Chesney, M. A. (2015). Preventing Loss of Independence through Exercise (PLIÉ): A pilot clinical trial in older adults with dementia. *PLoS ONE*, 10(2), e0113367. doi: 10.1371/journal.pone.0113367
- Barnes, D.E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology*, 10, 819–828. doi: 10.1016/S1474-4422(11)70072-2
- Barnett, J.H., Scoriels, L., & Munafò, M.R. (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biological Psychiatry*, 64, 137-144. doi: 10.1016/j.biopsych.2008.01.005
- Barral, S., Cosentino, S., Costa, R., Andersen, S.L., Christensen, K., Eckfeldt, J.H., ... & Mayeux, R. (2013). Exceptional memory performance in the Long Life Family Study (LLFS). *Neurobiology of Aging*, 34, 2445–2448. doi: 10.1016/j.neurobiolaging.2013.05.002
- Birren, J.E., & Cunningham, W. (1985) Research on the psychology of aging: Principles, concepts and theory. In J.E. Birren & K.W. Schaie (Eds.), *Handbook of the psychology of aging* (2nd ed., pp. 3-34) New York, NY: Van Nostrand Reinhold.
- Borroni, B., Alberici, A., Cercignani, M., Premi, E., Serra, L., Cerini, C. ... Bozzali, M. (2012). Granulin mutation drives brain damage and reorganization from preclinical to symptomatic FTL. *Neurobiology of Aging*, 33, 2506-2520. doi: 10.1016/j.neurobiolaging.2011.10.031

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Brainerd C.J., Reyna V.F., Petersen, R.C., Smith, G.E., & Taub, E.S. (2011). Is the apolipoprotein E genotype a biomarker for mild cognitive impairment? Findings from a nationally representative study. *Neuropsychology*, 25, 679–689. doi: 10.1037/a0024483
- Brown, C.L., Robitaille, A., Zelinski, E.M., Dixon, R.A., Hofer, S.M., & Piccinin, A. (2016). Cognitive activity mediates the association between social activity and cognitive performance: A longitudinal study. *Psychology and Aging*, 31(8), 831-846.
<http://dx.doi.org/10.1037/pag000134>.
- Cabeza, R., Albert, M., Belleville, S, Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., & Raja, M.N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, 19, 701-710.
- Caplan, L.J., & Schooler, C. (2003). The roles of fatalism, self-confidence, and intellectual resources in the disablement process in older adults. *Psychology and Aging*, 18, 551-561. [10.1037/0882-7974.18.3.551](https://doi.org/10.1037/0882-7974.18.3.551)
- Carlson, M.C., Kuo, J.H., Chuang, Y.-F., Varma, V., Harris, G., Albert, M., ..., & Fried, L. (2015). Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. *Alzheimer's and Dementia*, 11, 1340-1348. doi: 10.1016/j.jalz.2014.12.005
- Carrasquillo, M.M., Crook, J.E., Pedraza, O., Thomas, C.S., Pankratz, V.S., Allen, M., ... Ertekin-Taner, N. (2015). Late-onset Alzheimer risk variants in memory decline, incident mild cognitive impairment and Alzheimer disease. *Neurobiology of Aging*, 36, 60–67. doi: 10.1016/j.neurobiolaging.2014.07.042
- Caselli, R. J., Marchant, G. E., Hunt, K. S., Henslin, B. R., Kosiosek, H. E., Langbaum, J., ... Dueck, A. C. (2015). Predictive testing for Alzheimer's disease: Suicidal ideation in healthy participants. *Alzheimer Disease and Associated Disorders*, 29(3), 252–254. doi: 10.1097/WAD.0000000000000097
- Clarke, T.C., Norris, T. and Schiller, J.S. (2017) *Early Release of Selected Estimates Based on Data From the 2016 National Health Interview Survey*.
- Clem, M. A., Holliday, R. P., Pandya, S., Hynan, L. s., Lacritz, L. H. & Woon, F. L (2017) Predictors that a diagnosis of mild cognitive impairment will remain stable 3 years later.

CHAPTER 8: RISK AND PROTECTIVE FACTORS

Cognitive Behavioral Neurology, 30, 8-15.

- Corder, K., Ogilvie, D., & van Sluijs, E.M. (2009). Invited commentary: physical activity over the life course – Whose behavior changes, when, and why? *American Journal of Epidemiology*, 170, 1078-1081. doi: 10.1093/aje/kwp273
- Cosco, T.D., Prina, A.M., Perales, J., Stephan, B.C., & Brayne, C. (2014) Operational definitions of successful aging: A systematic review. *International Psychogeriatrics*, 26, 373-381. doi: 10.1017/S1041610213002287
- Cummings, J.L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimer's Research & Therapy*, 6(4), 37. doi: 10.1186/alzrt269
- Daffner, K.R. (2010). Promoting successful cognitive aging: A comprehensive review. *Journal of Alzheimer's Disease*, 19, 1101-1122. doi: 10.3233/JAD-2010-1306
- Darst, B.F., Kosciak, R.L., Racine, A.M., Oh, J.M., Krause, R.A., Carlsson, ... Engelman, C.D. (2017). Pathway-specific polygenic risk scores as predictors of β -amyloid deposition and cognitive function in a sample at increased risk for Alzheimer's disease. *Journal of Alzheimer's Disease*, 55, 473-484. doi: 10.3233/JAD-160195
- Das, D., Tan, X., Bielak, A.A., Cherbuin, N., Eastaer, S., & Anstey, K.J. (2014). Cognitive ability, intraindividual variability, and common genetic variants of catechol-O-methyltransferase and brain-derived neurotrophic factor: a longitudinal study in a population-based sample of older adults. *Psychology and Aging*, 29, 393-403. doi: 10.1037/a0035702
- Daugherty, A. M., Zwilling, C., Paul, E. J., Sherepa, N., Allen, C., Kramer, A. F., Hillman, C. H., Cohen, N. J., & Barbey, A. K. (2018). Multimodal fitness and cognitive training to enhance fluid intelligence. *Intelligence*, 66, 32-43.
- Daviglus, M.L., Bell, C.C., Berrettini, W., Bowen, P.E., Connolly, E.S., Cox, N.J., ... & Patel, D. (2010). National Institutes of Health State-of-the-Science Conference statement: Preventing Alzheimer disease and cognitive decline. *Annals of Internal Medicine*, 153, 176-181. doi: 10.7326/0003-4819-153-3-201008030-00260
- de Frias, C.M., & Dixon, R.A. (2014). Lifestyle engagement affects cognitive status differences and trajectories on executive functions in older adults. *Archives of Clinical Neuropsychology*, 29, 16-25. doi: 10.1093/arclin/act089

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- de Frias, C.M., Dixon, R.A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: From cognitively elite to cognitively impaired. *Neuropsychology*, 23, 778-791. doi: 10.1037/a0016743
- de Souto Barreto, P., Delrieu, J., Andrieu, S., Vellas, B., & Rolland, Y. (2016). Physical activity and cognitive function in middle-aged and older adults: An analysis of 104,909 people from 20 countries. *Mayo Clinic Proceedings*, 91, 1515-1524. doi: 10.1016/j.mayocp.2016.06.032
- Depp, C.A., Harmell, A., & Vahia, I.V. (2012). Successful cognitive aging. *Current Topics in Behavioral Neurosciences*, 10, 35–50. doi: 10.1007/7854_2011_158
- Depp, C.A., & Jeste, D.V. (2006). Definitions and predictors of successful aging: A comprehensive review of larger quantitative studies. *American Journal of Geriatric Psychiatry*, 14, 6-20. doi: 10.1097/01.JGP.0000192501.03069.bc
- Dixon, R.A. (2010). An epidemiological approach to cognitive health in aging. In L. Bäckman & L. Nyberg (Eds.), *Memory, aging, and the brain* (pp. 144-166). London: Psychology Press.
- Dixon, R.A. (2011). Enduring theoretical themes in psychological aging: Derivation, functions, perspectives, and opportunities. In K.W. Schaie & S.L. Willis (Eds.), *Handbook of the psychology of aging* (7th ed., pp. 3-23). San Diego, CA: Academic Press
- Dixon, R.A. & de Frias, C.M. (2007). Mild memory deficits differentially affect six-year changes in compensatory strategy use. *Psychology and Aging*, 22, 632-638. doi: 10.1037/0882-7974.22.3.632
- Dixon, R.A., & de Frias, C.M. (2014). Cognitively elite, cognitively normal, and cognitively impaired aging: Neurocognitive status and stability moderate memory performance. *Journal of Clinical and Experimental Neuropsychology*, 36, 418-430. doi: 10.1080/13803395.2014.903901
- Dixon, R.A., DeCarlo, C.A., MacDonald, S.W.S., Vergote, D., Jhamandas, J., & Westaway, D. (2014). *APOE* and *COMT* polymorphisms are complementary biomarkers of status, stability, and transitions in normal aging and early mild cognitive impairment. *Frontiers in Aging Neuroscience*, 6, 236. doi: 10.3389/fnagi.2014.00236
- Dixon, R.A., Garrett, D., & Bäckman, L. (2008). Principles of compensation in cognitive neuroscience and neurorehabilitation. In D.T. Stuss, G. Winocur, & I.H. Robertson

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- (Eds.), *Cognitive neurorehabilitation* (2nd ed.; pp. 22-38). Cambridge: Cambridge University Press
- Dixon, R.A., McFall, G.P. & McDermott, K. (2017, July). *Discriminating and predicting cognitive exceptionalism and resilience: A roadmap for trajectory and interaction analyses with risk and protection factors*. Paper presented at Alzheimer's Association International Conference, London, England.
- Dixon, R.A., Small, B.J., MacDonald, S.W.S., & McArdle, J.J. (2012). Yes, memory declines with aging--but when, how, and why? In M. Naveh-Benjamin & N. Ohta (Eds.), *Memory and Aging* (pp. 325-347). New York, NY: Psychology Press.
- Dotson, V. M., Beydoun, M. A., & Zonderman, A. B. (2010). Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology*, 75(1), 27–34. doi: 10.1212/WNL.0b013e3181e62124
- Edwards, M.K., & Loprinzi, P.D. (2017). The association between sedentary behavior and cognitive function among older adults may be attenuated with adequate physical activity. *Journal of Physical Activity and Health*, 14, 52-58. doi: 10.1123/jpah.2016-0313
- Ellwardt, L., Aartsen, M., Deeg, D., & Steverink, N. (2013). Does loneliness mediate the relation between social support and cognitive functioning in later life? *Social Science & Medicine*, 98, 116-124. doi: 10.1016/j.socscimed.2013.09.002
- Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., & Cawthon, R.M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 17312-17315. doi: 10.1073/pnas.0407162101
- Erickson, K.I., Hillman, C.H., & Kramer, A.F. (2015). Physical activity, brain, and cognition. *Current Opinion in Behavioral Sciences*, 4, 27-32. doi: 10.1016/j.cobeha.2015.01.005
- Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., ... Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, 19(10), 1030–1039. doi: 10.1002/hipo.20547

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Ferrari, R., Dawoodi, S., Raju, M., Thumma, A., Hynan, L. S., Maasumi, S. H., ... Momeni, P. (2013). Androgen receptor gene and gender specific Alzheimer's disease. *Neurobiology of Aging*, 34(8), 2077.e19–2077.e20. doi: 10.1016/j.neurobiolaging.2013.02.017
- Fiocco, A.J., & Yaffe, K. (2010). Defining successful aging: the importance of including cognitive function over time. *Archives of Neurology*, 67, 876–880. doi: 10.1001/archneurol.2010.130
- Fotuhi, M., Hachinski, V., & Whitehouse, P. J. (2009). Changing perspectives regarding late-life dementia. *Nature Reviews Neurology*, 5, 649-658.
- Foubert-Samier, A., Le Goff, M., Helmer, C., Pérès, K., Orgogozo, J.M., Barberger-Gateau, P., ... Dartigues, J. F. (2014). Change in leisure and social activities and risk of dementia in elderly cohort. *The Journal of Nutrition, Health & Aging*, 18, 876-882. doi: 10.1007/s12603-014-0475-7
- Fried, L.P., Carlson, M.C., Freedman, M., Frick, K.D., Glass, T.A., Hill, J., ... Zeger, S. (2004). A social model for health promotion for an aging population: Initial evidence on the Experience Corps model. *Journal of Urban Health*, 81, 64-78.
- Fried, L.P., Carlson, M.C., McGill, S., Seeman, T., Xue, Q.-L., Frick, K., ... Rebok, G.W. (2013). Experience Corps: A dual trial to promote the health of older adults and children's academic success. *Contemporary Clinical Trials*, 36, 1-13. doi: 10.1016/j.cct.2013.05.003
- Gaiteri, C., Mostafavi, S., Honey, C., De Jager, P.L., & Bennett, D.A. (2016). Genetic variants in Alzheimer disease – molecular and brain network approaches. *Nature Reviews. Neurology*, 12, 413-427. doi: 10.1038/nrneurol.2016.84
- Galbraith, S., Bowden, J., & Mander, A. (2017). Accelerated longitudinal designs: An overview of modelling, power, costs and handling missing data. *Statistical Methods in Medical Research*, 26(1), 374–398. <http://doi.org/10.1177/0962280214547150>
- Gefen, T., Shaw, E., Whitney, K., Martersteck, A., Stratton, J., Rademaker, A., ... Rogalski, E. (2014). Longitudinal neuropsychological performance of cognitive superagers. *Journal of the American Geriatrics Society*, 62, 1598–1600. doi: 10.1111/jgs.12967
- Glymour, M. M., & Manly, J. J. (2008). Lifecourse social conditions and racial and

CHAPTER 8: RISK AND PROTECTIVE FACTORS

ethnic patterns of cognitive aging. *Neuropsychological Review*, 18, 223-254.

- Gow, A.J., Pattie, A., & Deary, I.J. (2017). Lifecourse activity participation from early, mid, and later adulthood as determinants of cognitive Aging: the Lothian birth cohort 1921. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 72, 25-37. doi: 10.1093/geronb/gbw124 PMID: PMC5156497
- Graham, E.K., & Lachman, M.E. (2012). Personality stability is associated with better cognitive performance in adulthood: Are the stable more able? *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 67, 545-554. doi: 10.1093/geronb/gbr149
- Graham, E.K., & Lachman, M.E. (2014). Personality traits, facets and cognitive performance: Age differences in their relations. *Personality and Individual Differences*, 59, 89-95. doi: 10.1016/j.paid.2013.11.011
- Grossman, P., Niemann, L., Schmidt, S., & Walach, H. (2004). Mindfulness-based stress reduction and health benefits: A meta-analysis. *Journal of Psychosomatic Research*, 57, 35-43. doi: 10.1016/S0022-3999(03)00573-7
- Grzywacz, J.G., Segel-Karpas, D., & Lachman, M.E. (2016). Workplace exposures and cognitive function during adulthood: Evidence from national survey of midlife development and the O*NET. *Journal of Occupational & Environmental Medicine*, 58, 535-541. doi: 10.1097/JOM.0000000000000727
- Harris, S.E., & Deary, I.J. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Science*, 15, 388-394. doi: 10.1016/j.tics.2011.07.004
- Harrison, T.M., Weintraub, S., Mesulam, M.-M., & Rogalski, E. (2012). Superior memory and higher cortical volumes in unusually successful cognitive aging. *Journal of the International Neuropsychological Society*, 18, 1081-1085. doi: 10.1017/S1355617712000847
- Haslam, C., Cruwys, T., Milne, M., Kan, C.H., & Haslam, S.A. (2016). Group ties protect cognitive health by promoting social identification and social support. *Journal of Aging and Health*, 28, 244-266. doi: 10.1177/0898264315589578

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Herlitz, A., & Rehnman, J. (2008). Sex differences in episodic memory. *Current Directions in Psychological Science*, 17, 52-56. doi: 10.1111/j.1467-8721.2008.00547.x
- Hertzog, C., Dixon, R.A., & Hultsch, D.F. (1990). Metamemory in adulthood: Differentiating knowledge, belief, and behavior. *Advances in Psychology*, 71, 161-212. doi: 10.1016/S0166-4115(08)60158-2
- Hertzog, C., Kramer, A.F., Wilson, R.S., & Lindenberger, U. (2008). Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychological Science in the Public Interest*, 9, 1-65. doi: 10.1111/j.1539-6053.2009.01034.x
- Hess, T.M., Auman, C., Colcombe, S.J., & Rahhal, T.A. (2003). The impact of stereotype threat on age differences in memory performance. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 58, P3-P11.
- Hillman, C.H., Erickson, K.I., & Kramer, A.F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews. Neuroscience*, 9, 58-65.
- Hughes, M. L., Agrigoroaei, S., Jeon, M., Bruzzese, M., & Lachman, M. E. (2018). Change in cognitive performance from midlife into old age: Findings from the Midlife in the United States (MIDUS) Study. *Journal of the International Neuropsychological Society*, 24, 805-820. Online publication Jul 18 2018. doi: 10.1017/S1355617718000425
- Hughes, M.L., & Lachman, M.E. (2016). Social comparisons of health and cognitive functioning contribute to changes in subjective age. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*. doi: 10.1093/geronb/gbw044
- Hurd, M.D., Martorell, P., Delavande, A., Mullen, K.J., & Langa, K.M. (2013). Monetary costs of dementia in the United States. *The New England Journal of Medicine*, 368, 1326-1334.
- Ighodaro, E.T., Abner, E.L., Fardo, D.W., Lin, A.L., Katsumata, Y., Schmitt, F.A., ... & Kukull, W.A. (2017). Risk factors and global cognitive status related to brain arteriolosclerosis in elderly individuals. *Journal of Cerebral Blood Flow & Metabolism*, 37, 201-216. doi: 10.1177/0271678X15621574
- Institute of Medicine. 2015. *Cognitive Aging: Progress in understanding and opportunities for action*. Washington DC: The National Academies Press.

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Jack, C.R., Wiste, H.J., Weigand, S.D., Knopman, D.S., Vemuri, P., Mielke, M.M., ... Petersen, R.C. (2015). Age, sex and APOE ϵ 4 effects on memory, brain structure and β -amyloid across the adult lifespan. *JAMA Neurology*, 72, 511–519. doi: 10.1001/jamaneurol.2014.4821
- Johansson, L., Guo, X., Dubertstein, P. R., Hallstrom, T., Waern, M., Ostling, S., & Skoog, I. (2014). Midlife personality and risk of Alzheimers Disease and distress: A 38year followup. *Neurology*, 83, DOI: <https://doi.org/10.1212/WNL.0000000000000907>
- Jones, R.N., Manly, J., Glymour, M.M., Rentz, D.M., Jefferson, A.L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society*, 17, 593–601. doi: 10.1017/S1355617710001748
- Josefsson, M., de Luna, X., Pudas, S., Nilsson, L. G., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatrics Society*, 60, 2308-2312. doi: 10.1111/jgs.12000
- Karlamangla, A.S., Miller-Martinez, D., Lachman, M.E., Tun, P.A., Koretz, B.K., & Seeman, T.E. (2014). Biological correlates of adult cognition: Midlife in the United States (MIDUS). *Neurobiology of Aging*, 35, 387-394. doi: 10.1016/j.neurobiolaging.2013.07.028
- Kaup, A.R., Nettiksimmons, J., Harris, T.B., Sink, K.M., Satterfield, S., Metti, A.L., ... For the Health, Aging, and Body Composition (Health ABC) Study. (2015). Cognitive resilience to Apolipoprotein E ϵ 4: Contributing factors in black and white older adults. *JAMA Neurology*, 72, 340–348. doi: 10.1001/jamaneurol.2014.3978
- Kennedy, D.O., Wightman, E.L., Reay, J.L., Lietz, G., Okello, E.J., Wilde, A., & Haskell, C.F. (2010). Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation. *The American Journal of Clinical Nutrition*, 91, 1590-1597. doi: 10.3945/ajcn.2009.28641
- Kohl, H.W., Craig, C.L., Lambert, E.V., Inoue, S., Alkandari, J.R., Leetongin, G., & Kahlmeier, S. (2012). The pandemic of physical inactivity: Global action for public health. *The Lancet*, 3800, 294-305. doi: 10.1016/S0140-6736(12)60898-8

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Kraft, E. (2012). Cognitive function, physical activity, and aging: Possible biological links and implications for multimodal interventions. *Aging, Neuropsychology, and Cognition*, 19, 248-263. doi: 10.1080/13825585.2011.645010
- Kramer, A.F., Erickson, K.I., & Colcombe, S.J. (2006). Exercise, cognition, and the aging brain. *Journal of Applied Physiology*, 101, 1237-1242. doi: 10.1152/jappphysiol.00500.2006
- Kremen, W. S., Panizzon, M. S., & Cannon, T. D. (2016). Genetics and neuropsychology: A merger whose time has come. *Neuropsychology*, 30, 1-5. doi: 10.1037/neu0000254
- Lachman, M.E. (2006). Perceived control over aging-related declines: Adaptive beliefs and behaviors. *Current Directions in Psychological Science*, 15, 282-286. doi: 10.1111/j.1467-8721.2006.00453.x
- Lachman, M.E., & Agrigoroaei, S. (2010). Promoting functional health in midlife and old age: Long-term protective effects of control beliefs, social support, and physical exercise. *PLoS ONE*, 5. doi: 10.1371/journal.pone.0013297
- Lachman, M.E., Agrigoroaei, S., Murphy, C., & Tun, P.A. (2010). Frequent cognitive activity compensates for education differences in episodic memory. *American Journal of Geriatric Psychiatry*, 18, 4-10. doi: 10.1097/JGP.0b013e3181ab8b62
- Lachman, M.E., & Andreoletti, C. (2006). Strategy use mediates the relationship between control beliefs and memory performance for middle-aged and older adults. *Journal of Gerontology: Psychological Sciences*, 61B, P88-P94.
- Lachman, M.E., & Leff, R. (1989). Perceived control and intellectual functioning in the elderly: A 5-year longitudinal study. *Developmental Psychology*, 25, 722-728.
- Lachman, M.E., Neupert, S.D., & Agrigoroaei, S. (2011). The relevance of control beliefs for health and aging. In K. W. Schaie & S. L. Willis (Eds.), *Handbook of the psychology of aging* (7th ed., pp. 175-190). New York: Elsevier.
- Laitman, B.M., & John, G.R. (2015). Understanding how exercise promotes cognitive integrity in the aging brain. *PLoS Biology*, 13, e1002300. doi: 10.1371/journal.pbio.1002300, PMID: PMC4641709
- Langa, K.M., Larson, E.B., Crimmins, E.M., Faul, J.D., Levine, D.A., Kabeto, M.U., & Weir, D.R. (2017). A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Internal Medicine*, 177, 51-58. doi: 10.1001/jamainternmed.2016.6807

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Levy, B.R., Zonderman, A.B., Slade, M.D., & Ferrucci, L. (2011). Memory shaped by age stereotypes over time. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 67, 432-436. doi: 10.1093/geronb/gbr120
- Liao, J., Head, J., Kumari, M., Stansfeld, S., Kivimaki, M., Singh-Manoux, A., & Brunner, E.J. (2014). Negative aspects of close relationships as risk factors for cognitive aging. *American Journal of Epidemiology*, 180, 1118-1125. doi: 10.1093/aje/kwu236, PMID: PMC4239796
- Lindenberger, U., Nagel, I.E., Chicherio, C., Li, S.-C., Heekeren, H.R., & Bäckman, L. (2008). Age-related decline in brain resources modulates genetic effects on cognitive functioning. *Frontiers in Neuroscience*, 2, 234-244. doi: 10.3389/neuro.01.039.2008
- Litwin, H., Schwartz, E., & Damri, N. (2017). Cognitively stimulating leisure activity and subsequent cognitive function: A SHARE-based analysis. *The Gerontologist*, 57, 940-948. doi: 10.1093/geront/gnw084
- Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., ... & Cooper, C. (2017). Dementia prevention, intervention, and care. *The Lancet*. doi: 10.1016/S0140-6736(17)31363-6
- Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nature Reviews. Neurology*, 9, 106-118. doi: 10.1038/nrneurol.2012.263
- Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I.A., Ukoumunne, O.C., & Llewellyn, D.J. (2013). Mediterranean diet, cognitive function, and dementia: A systematic review. *Epidemiology*, 24, 479-489. doi: 10.1097/EDE.0b013e3182944410
- Lupien, S.J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T.E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and cognition*, 65, 209-237. doi: 10.1016/j.bandc.2007.02.007
- Lupien, S.J., McEwen, B.S., Gunnar, M.R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews. Neuroscience*, 10, 434-445.
- Macready, A.L., Kennedy, O.B., Ellis, J.A., Williams, C.M., Spencer, J.P.E., & Butler, L.T. (2009). Flavonoids and cognitive function: A review of human randomized controlled

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- trial studies and recommendations for future studies. *Genes & Nutrition*, 4, 227-242. doi: 10.1007/s12263-009-0135-4
- Mandelman, S.D., & Grigorenko, E.L. (2012). *BDNF* Val66Met and cognition: All, none, or some? A meta-analysis of the genetic association. *Genes, Brain, and Behavior*, 11, 127-136. doi: 10.1111/j.1601-183X.2011.00738.x
- Manly, J.J., Jacobs, D.M., Touradji, P., Small, S.A., & Stern, Y. (2002). Reading level attenuates differences in neuropsychological test performance between African American and White elders. *Journal of the International Neuropsychological Society*, 8, 341-348. doi: 10.1017/S1355617702813157
- Marioni, R.E., Proust-Lima, C., Amieva, H., Brayne, C., Matthews, F.E., Dartigues, J.F., & Jacqmin-Gadda, H. (2015). Social activity, cognitive decline and dementia risk: A 20-year prospective cohort study. *BMC Public Health*, 15, 1089. doi: 10.1186/s12889-015-2426-6, PMCID: PMC4619410
- Marioni, R.E., Valenzuela, M.J., van den Hout, A., Brayne, C., Matthews, F.E., & MRC Cognitive Function and Ageing Study. (2012). Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS ONE*, 7, e50940. doi: 10.1371/journal.pone.0050940
- Martínez-Lapiscina, E.H., Clavero, P., Toledo, E., Estruch, R., Salas-Salvadó, J., San Julián, B., ... Martínez-González, M.Á. (2013). Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomized trial. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84, 1318-1325. doi: 10.1136/jnnp-2012-304792
- McDermott, K., McFall, G.P., Andrews, S., Anstey, K.J., & Dixon, R.A. (2017). Memory resilience to Alzheimer's genetic risk: Sex effects in predictor profiles. *Journal of Gerontology: Psychological Sciences*, 72, 937-946. doi: 10.1093/geronb/gbw161
- McFall, G.P., Sapkota, S., McDermott, K.L., & Dixon, R.A. (2016). Risk-reducing apolipoprotein E and clusterin genotypes protect against the consequences of poor vascular health on executive function performance and change in non-demented older adults. *Neurobiology of Aging*, 42, 91-100. doi:10.1016/j.neurobiolaging.2016.02.032
- McFall, G.P., Wiebe, S.A., Vergote, D., Westaway, D., Jhamandas, J., Bäckman, L., & Dixon, R.A. (2015). ApoE and pulse pressure interactively influence level and change in the

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- aging of episodic memory: Protective effects among $\epsilon 2$ carriers. *Neuropsychology*, 29, 388-401. doi: 10.1037/neu0000150
- Murrell, J. R., Price, B., Lane, K. A., Baiyewu, O., Gureje, O., Ogunniyi, A., ... Hall, K. S. (2006). Association of apolipoprotein E genotype and Alzheimer disease in African Americans. *Archives of Neurology*, 63(3), 431–434. doi: 10.1001/archneur.63.3.431
- National Academies of Sciences, Engineering, and Medicine. 2017. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington, DC: The National Academies Press. doi: 10.17226/24782
- National Center for Health Statistics. Health, United States (2010): *With Special Feature on Death and Dying*. Hyattsville, MD. 2011.
- Neupert, S.D., Whitbourne, S.B., & Lachman, M.E. (2009). Exercise self-efficacy and control beliefs: Effects on exercise behavior after an exercise intervention for older adults. *Journal of Aging and Physical Activity*. doi: 10.1016/j.psychsport.2010.04.004
- Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., ... Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet*, 385, 2255-2263. doi: 10.1016/S0140-6736(15)60461-5
- Northey, J.M., Cherbuin, N., Pampa, K.L., Smee, D.J., & Rattray, B. (2017). Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-analysis. *British Journal of Sports Medicine*. doi: 10.1136/bjsports-2016-096587
- Papenberg, G., Lindenberger, U., & Bäckman, L. (2015). Aging-related magnification of genetic effects on cognitive and brain integrity. *Trends in Cognitive Sciences*, 19, 506-514. doi: 10.1016/j.tics.2015.06.008
- Parisi, J.M., Gross, A.L., Marsiske, M., Willis, S.L., & Rebok, G.M. (2017). Control beliefs and cognition over a 10-year period: Findings from the ACTIVE trial. *Psychology and Aging*, 32, 69-75. doi: 10.1037/pag0000147
- Park, D.C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G.N., & Aamodt, W. (2014). The impact of sustained engagement on cognitive function in older adults: The synapse project. *Psychological Science*, 25, 103-112. doi: 10.1177/0956797613499592
- Peters, R., Peters, J., Booth, A., & Mudway, I. (2015). Is air pollution associated with increased

CHAPTER 8: RISK AND PROTECTIVE FACTORS

risk of cognitive decline? A systematic review. *Age and Ageing*, 44(5), 755-760.

Plassman, B.L., Williams, J.W., Burke, J.R., Holsinger, T., & Benjamin, S. (2010). Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine*, 153, 182-193. doi: 10.7326/0003-4819-153-3-201008030-00258

Powell, K.E., Paluch, A.M., & Blair, S.N. (2011) Physical activity for health: What kind? How much? How intense? On top of what? *Annual Review of Health*, 32, 349-365. doi: 10.1146/annurev-publhealth-031210-101151

Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., & Karagiannidou, M. (2016). *World Alzheimer's Report 2016: Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future*. London, England: Alzheimer's Disease International.

Pruchno, R. (2015). Successful aging: Contentious past, productive future. *The Gerontologist*, 55, 1–4. doi: 10.1093/geront/gnv002

Pruchno, R.A., Wilson-Genderson, M., Rose, M., & Cartwright, F. (2010). Successful aging: Early influences and contemporary characteristics. *The Gerontologist*, 50(6), 821-833. doi: 10.1093/geront/gnq041

Raz, N., Rodrigue, K.M., Kennedy, K.M., & Land, S. (2009). Genetic and vascular modifiers of age-sensitive cognitive skills: Effects of COMT, BDNF, ApoE and hypertension. *Neuropsychology*, 23, 105–116. doi: 10.1037/a0013487

Rebok, G.W., Ball, K., Guey, L.T., Jones, R.N., Kim, H.Y., King, J.W., ... Willis, S.L. (2014). Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *Journal of the American Geriatrics Society*, 62, 16-24. doi: 10.1111/jgs.12607

Reuter- Lorenz, P. A. & Cappell, K. A. Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, 17, 177–182 (2008).

Reynolds, C.A., & Finkel, D. (2015). A meta-analysis of heritability of cognitive aging: Minding the "missing heritability" gap. *Neuropsychology Review*, 25, 97-112. doi: 10.1007/s11065-015-9280-2

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Richards, M., & Wadsworth, M.E.J. (2004). Long term effects of early adversity on cognitive function. *Archives of Disease in Childhood*, 89, 922-927. doi: 10.1136/ad.2003.032490
- Riedel, B.C., Thompson, P.M., & Brinton, R.D. (2016). Age, *APOE* and sex: Triad of risk of Alzheimer's Disease. *The Journal of Steroid Biochemistry and Molecular Biology*, 160, 134–147. doi: 10.1016/j.jsbmb.2016.03.012
- Robinson, S. A., Bisson, A. N., Hughest, M. L., Ebert, J., & Lachman, M. E. (2017). Time for Change: Implementation Intentions in an Exercise Intervention. Manuscript under review.
- Rogalski, E.J., Gefen, T., Shi, J., Samimi, M., Bigio, E., Weintraub, S., ... Mesulam, M.-M. (2013). Youthful memory capacity in old brains: Anatomic and genetic clues from the Northwestern SuperAging Project. *Journal of Cognitive Neuroscience*, 25, 29–36. doi: 10.1162/jocn_a_00300
- Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *The Gerontologist*, 37, 433–440.
- Sapkota, S., Vergote, D., Westaway, D., Jhamandas, J., & Dixon, R.A. (2015). Synergistic associations of COMT and BDNF with executive function in aging are selective and modified by APOE. *Neurobiology of Aging*, 36, 249-256. doi: 10.1016/j.neurobiolaging.2014.06.020
- Sapkota, S., Bäckman, L., & Dixon, R.A. (2017). In non-demented aging, executive function performance and change is predicted by apolipoprotein E, intensified by catechol-O-methyltransferase and brain-derived neurotrophic factor, and moderated by age and lifestyle. *Neurobiology of Aging*. 52, 81-89. doi: [10.1016/j.neurobiolaging.2016.12.022](https://doi.org/10.1016/j.neurobiolaging.2016.12.022).
- Sapkota, S., & Dixon, R.A. (2018). A network of genetic effects on non-demented cognitive aging: Alzheimer's genetic risk (CLU + CR1 + PICALM) intensifies cognitive aging genetic risk (COMT + BDNF) selectively for APOE ε4 carriers. *Journal of Alzheimer's Disease*, 62(2), 887-900. doi: 10.3233/JAD-170909
- Schaie, K.W. (1965). A general model for the study of developmental problems. *Psychological Bulletin*, 64, 92-107. doi: 10.1037/h0022371
- Schaie, K.W. (2012). *Developmental influences on adult intelligence: The Seattle longitudinal study* (2nd ed.). New York, NY: Oxford University Press.
- Schooler, C. (1999). The workplace environment: Measurement, psychological effects, and basic issues. In S.L. Friedman & T.D. Wachs (Eds.) *Measuring environment across the life*

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- span: Emerging methods and concepts* (pp. 229-246). Washington, DC: American Psychological Association.
- Scullin, M.K., & Bliwise, D.L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science, 10*, 97-137. doi: 10.1177/1745691614556680
- Searle, S. D., & Rockwood, K. (2015). Frailty and the risk of cognitive impairment. *Alzheimer's Research & Therapy, 7*(1), 54. doi: 10.1186/s13195-015-0140-3
- Seeman, T., Miller-Martinez, D., Stein-Merkin, S., Lachman, M.E., Tun, P., & Karlamangla, A. (2011). Histories of social engagement and adult cognition: Midlife in the U.S. Study. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 66B*, i141-i152. doi: 10.1093/geronb/gbq091
- Segel-Karpas, D., & Lachman, M.E. (2016). Social contact and cognitive functioning: The role of personality. *Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*. doi: 10.1093/geronb/gbw079
- Simon, S.S., Yokomizo, J.E., & Bottino, C.M. (2012). Cognitive intervention in amnestic Mild Cognitive Impairment: A systematic review. *Neuroscience & Biobehavioral Reviews, 36*, 1163-1178. doi: 10.1016/j.neubiorev.2012.01.007
- Sindi, S., Kåreholt, I., Johansson, L., Skoog, J., Söberg, L., Wang, H-X,... & Kivipelto, M. (2018). Sleep disturbances and dementia risk: A multicenter study. *Alzheimer's & Dementia, 14* (10), 1235–1242.
- Singh, B., Parsaik, A.K., Mielke, M.M., Erwin, P.J., Knopman, D.S., Petersen, R.C., & Roberts, R.O. (2014). Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. *Journal of Alzheimer's Disease, 39*, 271-282. doi: 10.3233/JAD-130830
- Small, B.J., Dixon, R.A., McArdle, J.J., & Grimm, K.J. (2012). Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the Victoria Longitudinal Study. *Neuropsychology, 26*, 144-155. doi: 10.1037/a0026579
- Small, B.J., Rosnick, C.B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology and Aging, 19*, 592-600. doi: 10.1037/0882-7974.19.4.592

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G.F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, 269, 107-117. doi: 10.1111/j.1365-2796.2010.02281.x
- Spiro, A., & Brady, C.B. (2011). Integrating health into cognitive aging: Toward a preventive cognitive neuroscience of aging. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 66B, i17–i25. doi: 10.1093/geronb/gbr018
- Stanford Center on Longevity (2014). “A Consensus on the Brain Training Industry from the Scientific Community,” Max Planck Institute for Human Development and Stanford Center on Longevity, accessed August 22, 2016, <http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-braintraining-industry-from-the-scientific-community/>
- Stephan, Y., Caudroit, J., Jaconelli, A., & Terracciano, A. (2014). Subjective age and cognitive functioning: A 10-year prospective study. *The American Journal of Geriatric Psychiatry*, 22, 1180-1187. doi: 10.1016/j.jagp.2013.03.007
- Stephan, Y., Sutin, A. r., Luchetti, M., & Terracciano, A. (2017). Feeling older and the development of cognitive impairment and dementia. *The Journals of Gerontology: Series B*, 72, 966–973, <https://doi.org/10.1093/geronb/gbw085>
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, 8, 448–460. doi: 10.1017/S1355617702813248
- Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47, 2015-2028. doi: 10.1016/j.neuropsychologia.2009.03.004
- Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, 11, 1006-1012. doi: 10.1016/S1474-4422(12)70191-6
- Sullivan, A.N., & Lachman, M.E. (2017). Behavior change with fitness technology in sedentary adults: A review of the evidence for increasing physical activity. *Frontiers in Public Health*, 4. doi: 10.3389/fpubh.2016.00289
- Tangney, C.C., Hong, L., Wang, Y., Barnes, L., Schneider, J.A., Bennett, D.A. & Morris, M.C. (2014). Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology*, 83, 1410-1416. doi: 10.1212/WNL.0000000000000884

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Terracciano, A., Stephan, Y., Luchetti, M., & Sutin, A.R. (2017). Cognitive impairment, dementia, and personality stability among older adults. *Assessment*. doi: 10.1177/1073191117691844
- Terracciano, A., Sutin, A.R., An, Y., O'Brien, R.J., Ferrucci, L. Zonderman, A.B., & Resnick, S.M. (2014). Personality and risk of Alzheimer's disease: New data and meta-analysis. *Alzheimer's & Dementia*, 10, 179-186. doi: 10.1016/j.jalz.2013.03.002
- Thibau, S., McFall, G.P., Camicioli, R., & Dixon, R.A. (2017). Alzheimer's disease biomarkers interactively influence physical activity, mobility, and cognition associations in a non-demented aging population. *Journal of Alzheimer's Disease*. 60, 69-86. doi: 10.3233/JAD-170130
- Thibau, S., McFall, G.P., Wiebe, S.A., Anstey, K.J., & Dixon, R.A. (2016). Genetic factors moderate everyday physical activity effects on executive function in aging: Evidence from the Victoria Longitudinal Study. *Neuropsychology*, 30(1), 6-17. doi: 10.1037/neu0000217
- Thorp, A.A., Owen, N., Neuhaus, M., & Dunstan, D.W. (2011). Sedentary behaviors and subsequent health outcomes in adults: A systematic review of longitudinal studies, 1996-2011. *American Journal of Preventive Medicine*, 41, 207-215. doi: 10.1016/j.amepre.2011.05.004
- Tierney, M.C., Curtis, A.F., Chertkow, H., & Rylett, R.J. (2017). Integrating sex and gender into neurodegeneration research: A six-component strategy. *Alzheimer's & Dementia: Translational Research & Clinical Intervention*, 3, 660-667. <https://doi.org/10.1016/j.trci.2017.10.006>
- Tucker-Drob, E.M., Reynolds, C.A., Finkel, D., & Pedersen, N.L. (2014). Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. *Developmental Psychology*, 50, 152-166. doi: 10.1037/a0032468
- Tun, P.A., Miller-Martinez, D., Lachman, M.E., & Seeman, T. (2013). Social strain and executive function across the lifespan: The dark (and light) sides of social engagement. *Aging, Neuropsychology, and Cognition*, 20, 320-338. doi: 10.1080/13825585.2012.707173
- van Loenhoud, A.C., Wink, A.M., Groot, C., Verfaillie, S.C.J., Twisk, J., Barkhof, F., ... Ossenkoppe, R. (2017). A neuroimaging approach to capture cognitive reserve:

CHAPTER 8: RISK AND PROTECTIVE FACTORS

- Application to Alzheimer's disease. *Human Brain Mapping*, 38, 4703–4715. doi: 10.1002/hbm.23695
- Varma, V.R., Chuang, Y.F., Harris, G.C., Tan, E.J., & Carlson, M.C. (2015). Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus*, 25, 605-615. doi: 10.1002/hipo.22397, PMCID: PMC4425252
- Vellas, B., Carrie, I., Gillette-Guyonnet, S., Touchon, J., Dantoine, T., Dartigues, J.F., ... Andrieu, S. (2014). MAPT study: A multidomain approach for preventing Alzheimer's disease: Design and baseline data. *The Journal of Prevention of Alzheimer's Disease*, 1, 13-22. doi: 10.14283/jpad.2014.34
- Wayne, P.M., Walsh, J.N., Taylor-Piliae, R.E., Wells, R.E., Papp, K.V., Donovan, N.J., & Yeh, G.Y. (2014). The impact of Tai Chi on cognitive performance in older adults: A systematic review and meta-analysis. *Journal of the American Geriatrics Society*, 62, 25-39. doi: 10.1111/jgs.12611
- Weber, D., Skirbekk, V., Freund, I., & Herlitz, A. (2014). The changing face of cognitive gender differences in Europe. *Proceedings of the National Academy of Sciences*, 111(32), 11673-11678.
- Wengreen, H., Munger, R.G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., ... Welsh-Bohmer, K.A. (2013). Prospective study of Dietary Approaches to Stop Hypertension- and Mediterranean-style dietary patterns and age-related cognitive change: The Cache County study on memory, health, and aging. *The American Journal of Clinical Nutrition*, 98, 1263-1271. doi: 10.3945/ajcn.112.051276
- Weuve, J., Puett, R.C., Schwartz, J., Yanosky, J.D., Laden, F., & Grodstein, F. (2012). Exposure to particulate air pollution and cognitive decline in older women. *Archives of Internal Medicine*, 172, 219-227. doi: 10.1001/archinternmed.2011.683
- Wimo, A., Guerchet, M., Ali, G.-C., Wu, Y.-T., Prina, A. M., Winblad, B., ... Prince, M. (2017). The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & Dementia*, 13(1), 1–7. doi: 10.1016/j.jalz.2016.07.150

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- Windsor, T.D., & Anstey, K.J. (2008). A longitudinal investigation of perceived control and cognitive performance in young, midlife and older adults. *Aging, Neuropsychology, and Cognition*, 15, 744-763. doi: 10.1080/13825580802348570
- Wisdom, N.M., Callahan, J.L., & Hawkins, K.A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging*, 32, 63-74. doi: 10.1016/j.neurobiolaging.2009.02.003
- World Health Organization. (2017). *Fact sheet: Physical activity*. Retrieved from <http://www.who.int/mediacentre/factsheets/fs385/en/>
- Yaffe, K., Fiocco, A.J., Lindquist, K., Vittinghoff, E., Simonsick, E.M., Newman, A.B., ... For the Health ABC Study (2009). Predictors of maintaining cognitive function in older adults: The Health ABC Study. *Neurology*, 72, 2029–2035. doi: 10.1212/WNL.0b013e3181a92c36
- Yaffe, K., Hoang, T.D., Byers, A.L., Barnes, D.E., & Friedl, K.E. (2014). Lifestyle and health-related risk factors and risk of cognitive aging among older veterans. *Alzheimer's & Dementia*, 10, S111-S121. doi: 10.1016/j.jalz.2014.04.010
- Zahodne, L. B., Glymour, M. M., Sparks, C., Bontempo, D., Dixon, R. A., MacDonald, S. W. S., & Manly, J. J. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. *Journal of the International Neuropsychological Society*, 17(6), 1039–1046. doi: 10.1017/S1355617711001044
- Zahodne, L.B., Manly, J.J., Azar, M., Brickman, A.M., & Glymour, M.M. (2016). Racial disparities in cognitive performance across mid and late adulthood: Analyses in two cohort studies. *Journal of the American Geriatrics Society*, 64, 959–964. doi: 10.1111/jgs.14113
- Zahodne, L.B., Sol, K., & Kraal, Z. (2017). Psychosocial pathways to racial/ethnic inequalities in late-life memory trajectories. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*. doi: 10.1093/geronb/gbx113
- Zeidan, F., Johnson, S.K., Diamond, B.J., David, Z., & Goolkasian, P. (2010). Mindfulness meditation improves cognition: Evidence of brief mental training. *Consciousness and Cognition*, 19, 597-605. doi: 10.1016/j.concog.2010.03.014

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- Zhang, C., & Pierce, B.L. (2014). Genetic susceptibility to accelerated cognitive decline in the US Health and Retirement Study. *Neurobiology of Aging*, 35, 1512.e11–1512.e18. doi: 10.1016/j.neurobiolaging.2013.12.021
- Zhao L., Mao Z., Woody S.K., & Brinton, R.D. (2016). Sex differences in metabolic aging of the brain: insights into female susceptibility to Alzheimer's disease. *Neurobiology of Aging*, 42, 69-79. doi: 10.1016/j.neurobiolaging.2016.02.011

Figure 1. Modifiable risk factors for Alzheimer’s disease and cognitive impairment, organized by life phase and ordered according to analyses and estimates from a recent review (based on Livingston et al., 2017). This comprehensive review (published in *The Lancet*) presents full information and further details.

A Model for Discriminating Pathways to Cognitive Resilience and Exceptionality

Figure 2. A model for discriminating pathways to (a) normal cognitive aging, (b) impaired or accelerated cognitive decline, (c) resilient cognitive aging, and (d) exceptional cognitive aging. This model is adapted from a presentation at the 2017 Alzheimer's Association International Conference (London) by Dixon, McFall, and McDermott (2017).