

## Translational Article

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# Mechanisms of Age-Related Cognitive Change and Targets for Intervention: Social Interactions and Stress

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**Background.** The effects of biological and physical factors on cognitive aging are widely studied. Less is known about the role of psychosocial factors such as stress and social relationships for cognitive functioning.

**Methods.** Speakers in Session IV of the Summit focused on possible mechanisms linking social interactions and stressful experiences to cognitive changes with aging.

**Results.** Elevated cortisol, repetitive thinking, negative emotions, neuroticism, chronic stress, and early life adversity were negatively associated with memory and other cognitive dimensions in later life. In contrast, supportive social relationships were found to be positively related to cognitive functioning. Some evidence was provided for multidirectional, causal relationships involving stress and negative affect as both antecedents and consequences of cognitive decline.

**Conclusions.** The findings contribute to understanding the potential underlying causal processes linking psychosocial factors and cognitive aging with a developmental focus on the etiology of declines and onset of cognitive impairments. This work provides an important foundation for future research to identify modifiable factors and to design interventions to minimize cognitive declines and optimize cognitive health in adulthood.

**Key Words:** Cognition—Aging—Social interactions—Stress.

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## INTRODUCTION AND OVERVIEW: THE ROLE OF PSYCHOSOCIAL FACTORS IN COGNITIVE AGING

There are many reliable findings showing that the frequency and quality of social interactions and reactions to stressful experiences are associated with cognitive functioning. Less is known, however, about how these variables are related to cognitive “changes.” Moreover, the causal nature and directionality of these relationships are unclear. Indeed, the report of the National Institutes of Health State-of-the-Science Conference on Alzheimer’s and Cognitive Decline Prevention in April 2010 stated, “Firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer’s Disease.” The contributors in this section present recent findings that will help

move us closer to articulating the relationship of social and stress variables to changes associated with cognitive aging.

W.S.K. discusses the association between stress and cognition and reports evidence for a bidirectional causal relationship. His contribution is enhanced with the use of data from twin studies. He finds the effects of cortisol go beyond episodic memory and apply also to other cognitive dimensions. M.S. considers the role of unconstructive repetitive thinking as an important psychosocial factor in the maintenance of chronic stress. He also advocates a longitudinal approach that would help move us closer to identifying the time course of the mechanisms linking stress and cognitive aging. R.S.W. examines the relationship of negative emotions and cognition. The analysis of neuroticism, anxiety, and depression

shows that they present a vulnerability to stress with effects on both episodic memory and executive functioning and that negative affect has damaging effects on the brain. All of these contributions help bring us closer to understanding mechanisms and to identifying potential targets for interventions. M.E.L. and J.C.P. provide an overview and integration of the topics, with introductory and concluding comments.

The effects of biological and physical factors such as health (eg, cardiovascular disease) and health behaviors (eg, physical exercise) on cognitive functioning are well known (1). Less is known about the role that psychosocial and behavioral factors play, yet there are many promising candidates. These include early life experiential factors (eg, educational attainment, childhood adversity), psychological factors (eg, personality, self-efficacy, control beliefs), stress exposure and reactivity, coping strategies, social factors (eg, social ties, network size, integration, support, and conflict), and behavioral factors such as engagement in cognitive activities or physical exercise. Yet, we do not have a clear understanding of how these psychosocial and behavioral factors get “under the skull.” The focus of this article is to consider some possible pathways linking cognitive functioning with social and stress variables, and whether modifying these factors could influence the course of cognitive aging.

Based on our review of the literature, some promising mechanisms that may link social and stress factors and cognitive aging are: hormonal factors (eg, cortisol, oxytocin), allostatic load (ie, multisystem dysregulation, including inflammation and metabolic parameters), neural plasticity, motivation, effort, strategy use, rumination, intrusive thinking, distraction, repetitive thought, and emotional factors such as depression, negative affect, and anxiety.

Many of the physiological effects discussed in this manuscript deal with the regulation of the hypothalamic-pituitary-adrenal (HPA) axis with its endproduct cortisol as a crucial mediating factor. Early life adversity is a potential root factor that is likely to have an impact on mechanisms and trajectories for cognitive aging. Thus, an appreciation of the developmental influences that shape individual differences in HPA axis activity and other key mechanisms is likely critical for our understanding the etiology of cognitive decline and the onset of cognitive impairments and dementia.

#### **A LONG-TERM BEHAVIOR GENETICS VIEW OF STRESS AND COGNITIVE AGING**

The twin design remains important in cognitive aging, in part, because we cannot assume *a priori* what is genetic or environmental. Psychosocial and genetic factors are typically thought of as largely separate domains, but even some dimensions of family environment scales have been shown to be heritable.

A unique feature of our study is that we have general cognitive ability scores at age 20 with repeated testing 35 years later (2). General cognitive ability is highly heritable. From young adulthood to late midlife, we found a very slight increase in heritability with some reduction in shared

environmental influences (2). Our longitudinal design also allowed us to show that the same genetic influences were operating on general cognitive ability at each time point. However, similar to later life cognitive changes, the amount of change between age 20 and 55 was accounted for by environmental factors (2). This is not always the case. For example, our longitudinal twin analysis of body mass index indicated that there are some different genetic influences operating on body mass index in midlife and young adulthood. These findings provide critical information for genetic association studies; the effect of age is not a factor in gene associations for general cognitive ability, but it is for body mass index (3). It remains to be seen whether there will be differential age-related changes in heritability in specific cognitive abilities.

Turning to stress and cognitive aging, we focused on daily cortisol levels as an index of stress responsivity or chronic stress exposure (4). Hippocampus and hippocampal-dependent memory have been the predominant focus in cortisol research. However, our analysis of 780 twins showed that, after controlling for age 20 general cognitive ability, higher cortisol levels were associated with poorer executive function, abstract reasoning, processing speed, and visual-spatial memory (5). These small but significant associations suggest that cortisol affects prefrontal as well as hippocampal function. Indeed, our Magnetic Resonance Imaging study of over 400 twins showed that higher cortisol levels were associated with thinner cortex in several prefrontal regions (but not with hippocampal volume), and some of the associations seemed to be due largely to shared genetic influences (3). These findings have important implications for stress and cognitive aging given that there is a high concentration of glucocorticoid receptors in prefrontal cortex, HPA axis function may become less efficient with increasing age, frontal lobe functions are susceptible to age effects, and the frontal lobes manifest more age-related shrinkage than other parenchymal regions (3).

A return to our long-term perspective suggests that the situation may be more complicated. Higher general cognitive ability at age 20 predicted lower cortisol levels at age 55 (5). This finding suggests that links between cortisol and cognition are not unidirectional. In other prospective twin and nontwin analyses, we have shown that general cognitive ability predicts later posttraumatic stress disorder and midlife depressive symptoms (6). In preliminary results presented at the Cognitive Aging Summit II, we also showed that early childhood adversity was a predictor of both age 20 cognitive ability and age 55 cortisol levels. Taken together, these findings suggest that general cognitive ability is a genetically mediated risk or protective factor for stress-related conditions that may, in turn, have further deleterious effects on cognitive function. Perhaps, higher cognitive ability lends itself to more adaptive coping strategies. Moreover, stress may have relatively early and lasting effects, suggesting that some processes we interpret as aging effects could actually reflect long-standing phenomena.

### **INTRAINDIVIDUAL VARIABILITY IN THE RELATIONSHIP BETWEEN STRESS AND COGNITIVE AGING**

Decades of research have linked stress to adverse physical and emotional health outcomes in aging adults. More recently, studies have identified stress-related variables as important predictors of cognitive aging. Stress is an important risk factor in this regard, both because it is a viable target for intervention and because it relates to a broad range of aging-related physical, mental, and cognitive health outcomes. However, there is considerable variability in the negative effects of stress, both within and across individuals. Characteristics of different stressors contribute to this variation, but individuals exposed to the same or similar stressors still exhibit substantial differences in their responses. Understanding the mechanisms that can account for this variability represents a critical challenge for explaining how stress affects cognitive health and for developing effective interventions.

Despite the empirical support linking stress-related variables to cognitive aging, two critical questions remain largely uninvestigated:

How do the effects of discrete stressful experiences accumulate to alter long-term cognitive aging trajectories? Under favorable conditions, the stress response is time-limited and serves an adaptive function by increasing alertness, mobilizing energy, and altering immune function. Prolonged exposure to the physiological and emotional concomitants of stressors, however, may lead to pathogenic states that codetermine structural and functional brain damage associated with aging. But persistent exposure to environmental challenges is not the only pathway leading to the experience of chronic stress. The inability to “shut off” the stress response after termination of the stressor represents another important pathway leading to the maintenance of chronic stress. For some individuals, the emotional and physiological effects of a stressor cease upon its removal, but for others, these effects may far outlive the actual stressor. Recurrent thinking about problematic situations and events can amplify and extend emotional and physiological responses, even after cessation of the eliciting stressor (7). Recent research suggests that unconstructive repetitive thought which encompasses related concepts such as worry, rumination, and preservative cognition operates as a final psychological pathway by which stressors exert their harmful effects (8) and can affect cognitive health in older adults (9).

Is “stress” both a cause and consequence of cognitive aging? Although most research postulates that stress plays an important causal role in aging-related cognitive loss, the evidence for this is more suggestive than conclusive. Most studies have been cross-sectional, and those with longitudinal follow-up have not examined the temporal ordering of stress and cognitive changes. Low or declining levels of cognition, particularly fluid abilities, may decrease a person’s resilience and hamper their ability to cope with everyday stressors resulting in amplified or prolonged stress responses (10). It may also be the case that age-graded declines in prefrontal cortex and hippocampal volume unrelated to stress degrade the effectiveness

of negative feedback control on HPA axis activity, resulting in increased cortisol output. Studies showing that baseline stress biomarkers predict cognitive decline cannot rule out the possibility that those baseline measures were influenced by concurrent or previous levels of cognitive functioning. Even, the few studies that have examined changes in both stress variables (eg, cortisol) and cognition have not evaluated alternative hypotheses regarding the temporal ordering of these changes. More fine-grained longitudinal assessments are required to better understand the timing and sequencing between stress and cognitive, which could identify targets for intervention strategies designed to promote cognitive health.

### **PSYCHOLOGICAL INFLUENCES ON COGNITIVE AGING**

Cognitive decline in old age is common and increases risk of adverse health outcomes. Because the U. S. population is aging, the scope of this problem is likely to increase in the coming decades, underscoring the need to identify factors contributing to age-related cognitive decline and strategies to minimize their impact.

Individuals differ in their tendency to experience negative emotions. This trait, variously referred to as neuroticism, negative affectivity, or emotional instability, is relatively stable in adulthood. As a result, its level in old age is a good indicator of the cumulative level of psychological stress experienced during the life span. In epidemiologic research, a higher level of this trait has been associated with more rapid cognitive decline in old age (11–14). The neuroticism trait also appears to account for much of the association of depressive symptoms with cognitive decline (15). The association is stronger for some facets of neuroticism (ie, anxiety, vulnerability to stress) and domains of cognition (ie, episodic memory, executive function; 11–14) than others.

It is possible that negative affect is a consequence of cognitive decline rather than a risk factor, but existing data are not supportive. First, negative affect in cognitively healthy older people predicts the initial appearance of cognitive impairment in old age (13). Second, depressive symptoms do not appear to substantially increase in older people when they develop cognitive impairment (16–18). Third, in clinical–pathological studies, the neuropathological lesions associated with incipient cognitive decline in old age (19) have not been associated with negative affect (11,15). At present, therefore, there is little support for a reverse causality explanation of the association of chronic negative affect with late life loss of cognition.

That negative affect is not associated with pathologic lesions linked to age-related cognitive decline suggests that other neurobiologic mechanisms are involved. In animals, chronic stress exposure is associated with a spectrum of changes in brain structure and function. These include reduced apical dendrite branching and dendritic spine density in hippocampus and elsewhere.

We used postmortem brain tissue from the Religious Orders Study to investigate whether chronic negative affect in aged humans was associated with similar dendritic changes. Semiautomated image acquisition and analysis was used

to quantify the densities of microtubule-associated protein 2-immunolabeled dendrites and synaptopodin-immunolabeled dendritic spines in the CA3 subfield of the hippocampus. Higher levels of anxiety and depression in the years prior to death were associated with lower densities of dendrites and spines in CA3 (20). This finding suggests that at least some of the neurobiological changes that accompany chronic stress in experimental animals may be related to chronic negative affect in humans. This observation is important because animal research suggests that chronic stress-related changes in the brain can be reduced by a range of factors including antidepressants, exercise, and dietary changes.

In summary, negative affect is associated with the initial stages of age-related cognitive decline by mechanisms that appear to be independent of common neuropathologic lesions linked to incipient loss of cognition in old age. Better understanding of the link between negative affect and cognitive dysfunction might inform strategies for modifying the adverse consequences of negative affect.

#### **UNDERSTANDING MECHANISMS: THE CAUSE AND CONSEQUENCE OF CORTISOL IN RELATION TO LIFETIME STRESS AND COGNITIVE DECLINE**

The question of the directionality of cortisol and aging is a frequently asked one and has been discussed by several of the speakers in the “social interactions and stress” section of the Cognitive Aging Summit II. Indeed, there are many good reasons to assume that it might be a bidirectional association. This, in part, has to do with the fact that cortisol regulation is determined in part by events early in life, but at the same time represents a target of chronic stress, making it difficult to interpret. To give an example, does a lower cortisol response to a standardized stressor mean that the participant suffers from hypocortisolemia as a consequence of chronic stress or was the individual’s response to that particular challenge always that low? However, some common observations lead to a working model that seem to be in line with available data, suggesting that (a) events early in life have a specific programming effect on the regulation of the HPA with implications for cognitive aging and dementia, (b) cognitive abilities in part determine the HPA axis responsivity to stress, by changing the threshold at which a participant is threatened by external events, and thus stressed, and (c) chronic stress throughout adulthood can lead to further adjustments in the regulation of the axis.

To comment on this a bit further, research in human and nonhuman participants has consistently reported detrimental effects of early life adversity on stress sensitivity and the ability to modulate stress responses across adulthood. Such findings suggest that the quality of mother–infant interactions regulate stress reactivity in the offspring throughout life. In earlier studies, evidence of such effects was shown by using retrospective reports of the quality of parental care, via the Parental Bonding Index, and employ it to predict individual differences in cortisol and central catecholamine (using Positron Emission Tomography imaging) response to stress (21).

In rodents, systematic variations in mother–infant interactions during early postnatal life have an enduring effect on the behavioral and HPA responses to stress (22) as well as on the mesolimbic dopamine stress responses. In addition, variations in maternal care in the rat are also associated with profound alterations in hippocampal synaptic development (23), suggesting that parental care in mammals might directly alter the structural development of corticolimbic regions involved in cognitive and emotional function, with consequences for cognitive ability and perhaps cognitive reserve. In humans, childhood abuse has been found to be directly related to the expression of those genes that determine stress regulation (ie, the glucocorticoid receptor). These findings point to some mechanisms that are related to both stress regulation and cognitive ability.

These findings are further consistent with recent studies in humans that reflect the importance of variations in parental care on cognitive development across adulthood and into old age. Recent data suggests that parental care can directly affect cognitive functions and that such effects are particularly apparent among high-risk children. Thus, a number of studies report increased parental effects on cognitive and emotional outcomes with children born at low birth weight. Interestingly, there are also greater effects of parenting intervention studies among more vulnerable children. Evidence that these early-life effects might affect structures associated with cognitive aging, and dementia was further contributed within the limitations of a cross-sectional retrospective design (24). Hippocampal volume, assessed using Magnetic Resonance Imaging and structural segmentation, was assessed as a function of birth weight (corrected for gestational age) and perceived quality of maternal care during the first 16 years of life (ie, Parental Bonding Index) in young adults. The hippocampus was the target region based on the relevance of this structure for stress regulation, cognition, memory, and as risk factor for dementia. Interestingly, the effect of low birth weight, as a proxy of prenatal adversity, on hippocampal volume was offset in participants that reported a high quality maternal care. Among participants that reported a low quality of maternal care, there was a significant positive correlation between birth weight and hippocampal volumes. Lower birth weight was associated with reduced hippocampal volume in adulthood. Participants with high maternal care showed no effect of birth weight on hippocampal volume. Although such retrospective reports are subject to criticism, it is interesting to note that even the retrospectively measured perceived quality of parental care in a small sample was still powerful enough to explain a significant amount of the variability in the data. It has previously been shown that the hippocampus, a known early marker for neurodegeneration and dementia, has a larger within than between age-cohort variability (25), so these results allow some interesting speculation about the origins of this variability, perhaps further relating to such concepts as cognitive reserve.

Perhaps, the most dramatic evidence for the influence of parental care comes from studies of abuse in childhood. In

humans, physical and/or sexual abuse in early life increases endocrine and autonomic responses to stress in adulthood. Children from high-conflict homes show increased cardiovascular reactivity and elevated basal cortisol. Among adults, early parental loss is associated with increased cardiovascular and HPA responses to stress, an effect that is mediated by the quality of the relation with the surviving parent. Increased cardiovascular and HPA responses to stress, in turn, have been found to be predictors of poor cardiovascular health and eventually lead to increased risk of neurodegenerative disease and dementia.

## ADVANCING OUR UNDERSTANDING OF COGNITIVE AGING PROCESSES

### *Identifying Mechanisms: Mediators and Moderators*

Much of the work linking psychosocial factors with cognition has focused on mediation and typically single mediator models. For example, in this article, R.S.W. considers stress as a link between negative affect and cognitive decline. To move beyond current models, in future work, it will be useful to consider multiple mediators, either simultaneously or in a complex causal chain. To illustrate by integrating several of the separate findings mentioned in this article, those with a greater sense of control may experience less stress reactivity, and in turn be less likely to experience anxiety and repetitive thoughts, resulting in better cognitive performance. Another useful approach to addressing mechanisms is to examine moderation. This entails interaction effects, which indicate factors that can moderate, attenuate, or buffer age-related declines. Age-related changes in cognition may be reduced for those who have low levels of stress or more supportive social relationships. There is some evidence in the literature that education-associated differences in cognitive performance can be reduced by engaging in frequent cognitive activity (26).

Another approach is to focus on multiple contributing factors in an additive fashion. Most studies look at one factor or if they consider several factors, they do so by looking at independent effects, that is, the contribution of each factor while controlling for the other factors. However, the effects of stress, social relationships, and other psychosocial and behavioral factors may be cumulative, or additive, similar to the effects of multisystem dysregulation or allostatic load. This suggests an approach that focuses on combined effects using a composite factor.

In the Boston Longitudinal subsample of the National Study of Midlife in the United States (MIDUS), Agrigoroaei and Lachman (27) explored the contribution of a psychosocial and behavioral composite to cognitive changes in fluid reasoning. The composite included factors from three domains: "Social" (good quality social relations—high support and low strain = 1); "Psychological" (high sense of control—high mastery and low constraints = 1); and "Physical/

Behavioral" (frequent vigorous physical exercise = 1). A composite ranging from 0 to 3 (low or high on each factor) was computed. Controlling for age, sex, education, race, waist circumference, smoking, alcohol problems, functional health, and frequency of cognitive activity, those with a higher composite score showed less decline in reasoning over a 10-year period. Thus, the composite showed protective effects for 10-year changes in fluid reasoning, with more adaptive psychosocial profiles predicting better cognitive outcomes.

### *Intervention Approaches*

If we identify promising factors such as social support, social engagement, cognitive activity, reduction of stress and repetitive thought, or low anxiety that are helpful for cognitive functioning, the findings may suggest useful targets for intervention. For intervention programs to be most effective, several criteria should be considered. Ideally, interventions should be multimodal, multifaceted, integrated into everyday life, preventive, and target vulnerable high-risk groups. One successful example of an intervention that follow this approach is: The Experience Corps (28), which found that older adults from low socioeconomic status backgrounds, who volunteered in inner city Baltimore schools, improved their cognitive and physical health. If we are to target social relationships with interventions, one question is whether to focus on improving existing social relations or cultivating new ones, as in the Experience Corps. Another interesting question is whether virtual relationships (eg, web-based chat rooms and support groups) are as effective as in vivo interactions for promoting cognitive health. For stress reduction, there are some promising signs from interventions that involve meditation and mindfulness training.

### *Conclusions*

The value of taking a multidisciplinary approach to cognitive aging is clear. It also worthwhile to integrate findings from epidemiological (survey) and experimental (lab) studies, to balance internal validity and generalizability of the results. To advance the field, we must obtain more precise and definitive data regarding directionality and causality. This will be facilitated by examining antecedents of intraindividual change, change processes, and variability with longitudinal prospective data. Another approach is to test mechanisms and treatment benefits with interventions, including randomized clinical trials. We also can consider ways to apply research findings about social relationships, stress, and cognitive plasticity to develop and implement new social policies. Although most expect to complete their formal education in early adulthood, there are needs and opportunities for learning throughout life. We can consider policies to facilitate lifelong education, work-related retraining in midlife, and longer and more varied work lives. Such changes in our practices could enrich our work and learning environments,

increase social interactions, and reduce stress, with a potential added benefit of improving cognitive health.

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