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Special Issue on Cognition and Behavioral Psychology

Session II: Mechanisms of Age-Related Cognitive Change and Targets for Intervention: Neural Circuits, Networks, and Plasticity

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Age-related changes in neural circuits, neural networks, and their plasticity are central to our understanding of age changes in cognition and brain structure and function. This paper summarizes selected findings on these topics presented at the Cognitive Aging Summit II. Specific areas discussed were synaptic vulnerability and plasticity, including the role of different types of synaptic spines, and hormonal effects in the dorsolateral prefrontal cortex of nonhuman primates, the impact of both compensatory processes and dedifferentiation on demand-dependent differences in prefrontal activation in relation to age and performance, the role of vascular disease, indexed by white matter signal abnormalities, on prefrontal activation during a functional magnetic resonance imaging-based cognitive control paradigm, and the influence of amyloid-β neuropathology on memory performance in older adults and the networks of brain activity underlying variability in performance. A greater understanding of age-related changes in brain plasticity and neural networks in healthy aging and in the presence of underlying vascular disease or amyloid pathology will be essential to identify new targets for intervention. Moreover, this understanding will assist in promoting the utilization of existing interventions, such as lifestyle and therapeutic modifiers of vascular disease.

Key Words: Cognitive changes—Aging—Neural networks.

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NEURAL circuits and networks, and their plasticity, are central to our understanding of brain function and changes in cognition with age. As discussed in other sections of this Special Issue, inflammatory, oxidative, and metabolic processes, genetic and epigenetic expression, and environmental exposures that include social interactions and stress affect these systems. It is important to understand the limits imposed by age and also where normal aging ends and disease begins. For example, the circulatory system ages in ways that can be harmful to the brain even in those who have not suffered a stroke or other vascular disease. Large numbers of older people develop subclinical vascular damage, such as covert infarcts, hemorrhages, or white matter lesions of which they are unaware. There is evidence that this subclinical vascular disease may account for changes in cognition often attributed to normal aging (1–3). Similarly, the study of normal cognitive aging in humans is complicated by the large proportion of people who appear to be aging successfully from a cognitive standpoint but have extracellular beta amyloid deposits that are the hallmark of Alzheimer's disease (AD).

In this section, researchers employ a variety of approaches to understand age-related cognitive changes and possible targets for intervention. John Morrison examines age-related synaptic vulnerability, plasticity, and hormonal effects in the dorsolateral prefrontal cortex of nonhuman primates. His investigations show that age-related loss of thin synaptic spines—so-called "learning spines"—is associated with poorer cognitive performance and that these changes can be partially reversed with estradiol treatment. Thus, endocrine senescence may be linked to neural aging,

and age-associated cognitive declines may be modifiable with hormonal targets. In human experiments, Patricia Reuter-Lorenz describes demand-dependent differences in prefrontal activation in relation to age and performance. Her results suggest overactivation of bilateral prefrontal cortex in prefrontal tasks may be compensatory in older adults but that when demand for cognitive resources exceeds supply, underactivation results and may explain some age-related losses of ability. In addition, dedifferentiation of circuits may play a role in individuals as they age and affect both specific and general circuits. The final two sections consider subclinical disease states (vascular and amyloid-related) as potentially modifiable factors that may contribute to age-associated declines. Charles DeCarli presents studies of white matter lesions, seen on brain imaging, and dorsolateral prefrontal cortical dysfunction. Functional imaging studies of individuals with high white matter lesion burden show a reduction in dorsolateral prefrontal cortical activity and reduced functional connectivity between brain regions. As potentially modifiable risk factors for vascular disease are thought to be an important cause of white matter lesions, these results support the hypothesis that cerebrovascular disease contributes to the disconnection of cortical circuits and the development of cognitive losses with aging. Finally, Reisa Sperling shows that cerebral amyloid deposition in cognitively normal elderly is associated with poorer neuropsychological performance compared with those without such deposition and that these changes are accompanied by alterations most evident in the default mode network.

John H. Morrison: Synaptic Correlates of Cognitive Performance—Implications for Cognitive Aging

In AD, cortical connections are dramatically altered as selectively vulnerable neurons die and circuits deteriorate. Many of the same cortical neurons and circuits are vulnerable in age-associated memory impairment; however, the vulnerability is manifested at synapses, not in neuron death (4). Furthermore, steroids (eg, estradiol) impact these same circuits, suggesting that endocrine senescence may be linked not only to neural aging but also that protection against age-related decline is feasible (5). We have been pursuing the synaptic basis of cognitive decline in both the dorsolateral prefrontal cortex (dlPFC) and hippocampus in young and aged rhesus monkeys that have undergone extensive behavioral testing to reveal age-related decrements in cognitive tasks linked to dlPFC and the medial temporal lobe system, both of which are affected by aging in monkeys (6). With respect to primate dlPFC, we have been particularly influenced by Earl Miller's conceptualization of dlPFC function, in that it is responsible for not only "establishing the rules" for goal-directed behavior but also for modifying those rules (7). We have hypothesized that such a role in cognitive function would require extensive ongoing synaptic plasticity, perhaps more than most cortical areas.

Recent in vivo imaging studies have shown that the thin spines on pyramidal cells are highly plastic and potentially transient, whereas the large mushroom spines are highly stable and likely mediate well-established synaptic pathways (8). From this perspective, thin spines have been referred to as "learning spines" and large mushroom spines as "memory spines" (8). Using quantitative reconstruction of Lucifer yellow loaded neurons in Layer 3 of dlPFC and electron microscopy analyses of dentate gyrus (DG), we have revealed several synaptic correlates of cognitive performance and age-related decline. In aged rhesus monkeys that are impaired on acquisition of delayed non-matching-to-sample, there is a 33% loss of spines on Layer 3 pyramidal cells in area 46 of dlPFC (9). Importantly, all of this spine loss is accounted for by loss of thin spines, which decrease by 45%, whereas other spine classes like mushroom spines are not affected by aging (9). In addition, the thin spines are smaller in young animals, suggesting that generation of new spines is particularly robust in young animals. Furthermore, although the number of thin spines correlates with cognitive performance in a given animal, there is no such correlation with mushroom spines, suggesting that the thin spines play a crucial role in cognitive tasks mediated by dlPFC that suffer with aging(9). In contrast, the stability of mushroom spines with aging may help explain the often-observed retention of well-established skills and knowledge referred to as expertise. The same class of thin spines that is vulnerable to aging is partially restored by estradiol treatment in ovariectomized female rhesus monkeys, suggesting that the loss of this spine class and associated cognitive decline may be preventable (5,10).

We used electron microscopic techniques to analyze the DG in the same animals, with particular attention to the perforant path terminal zone in the outer molecular layer (OML) of the DG, known to be highly vulnerable to aging (4). The pattern of synaptic aging differed dramatically from dlPFC, with no frank loss of total axospinous synapses, but instead, a loss of the very large, stable perforated synapses that was associated with menopause (11). Furthermore, the number of perforated synapses in the OML was predictive of performance on the delayed non-matching-to-sample task.

These data demonstrate the following. First, synaptic aging is different in dlPFC and DG OML, with a high degree of overall synaptic preservation in DG OML and extensive, yet selective, axospinous synapse loss in dlPFC. Second, synaptic correlates of cognitive performance differ in dlPFC and DG, with the small thin spines key in dlPFC and large stable spines/synapses (ie, perforated) key in OML of DG. Third, age-related cognitive decline in dlPFC is likely associated with a loss of spine/synapse formation, turnover, and structural plasticity, whereas this does not appear to be a major factor in DG OML. Our current hypothesis, to be tested further, is that cognitive performance mediated by dlPFC in primates requires new spines and synapse turnover, whereas the memory demands of hippocampus are more closely related to stabilization of existing synapses and molecular alterations of relatively stable synapses.

Patricia A. Reuter-Lorenz: Why Compensation-Related Utilization of Neural Circuits Hypothesis Matters: Compensation-Related Utilization of Neural Circuits Hypothesis, Aging, and Intervention

A common finding from functional brain imaging studies of cognitive aging is that older adults show more widespread activation than younger adults performing the same cognitive task (12,13). Such age-related overactivation is documented across perceptual, memory, verbal, spatial, and executive function tasks. Although the functional significance of overactivation may vary depending on task domain, brain region, or population, for higher-order executive type tasks that recruit prefrontal processes, there are strong indications that overactivation may be compensatory.

Accordingly, we have proposed the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) to explain demand-dependent age differences in prefrontal activation and how they relate to performance (12). CRUNCH builds on the initial discovery of bilateral prefrontal activation in older adults during both verbal and spatial working memory tasks, whereas younger adults show lateralized activation that is domain dependent (14). Bilateral activation, especially in ventro- and dorso-lateral prefrontal regions has been replicated during working memory and other higher-order tasks. We and others (14–16) originally favored a compensatory interpretation because prefrontal overactivation correlated positively with performance and its bilateral distribution characterized high performing seniors (12,17). Furthermore, converging behavioral evidence using lateralized stimulus presentations indicated performance benefits when older adults engage both hemispheres at lower levels of task demand (18).

CRUNCH recognizes, however, that even if overactivation is compensatory, the need to engage additional computational support may have a cost (12). That is, recruiting more resources at low levels of task demand, runs the risk of supply insufficiencies at high demand. CRUNCH therefore entails a resource ceiling and proposes a dynamic relationship between age and prefrontal activity that is determined by individual- and task-related factors (12). Figure 1 illustrates two hypothetical functions relating task demand or load to prefrontal activation. Because older adults are shifted to the left, they will reach their activation maximum (red arrow) or the circuit's saturation point with lower demand after which activation and performance decline because demand exceeds supply. Consequently, older adults operate within a narrower range of task demands compared with younger adults. Additional subject-related factors can be readily accommodated in this model. For example, high performing subgroups would be shifted rightward and low performers leftward with respect to their age group. Similarly, interventions that enhance neural efficiency should shift functions to the right, thereby increasing the range of task demand to which a system can respond. CRUNCH thus offers a framework to identify targets for intervention and for predicting outcomes (19). CRUNCH is in the tradition of cognitive resource theory and resource accounts of aging. However, unlike prior theories, it operationalizes resources in terms of specific interacting neural circuits that can provide new independent variables for hypothesis testing.

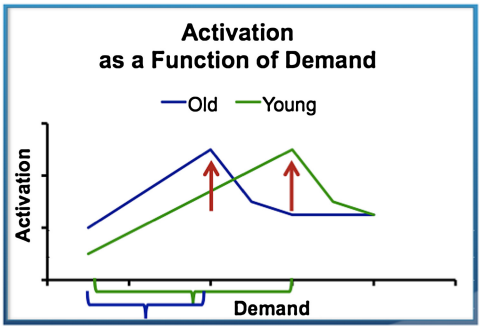

Figure 1.Activation as a function of task demand.

Several laboratories have reported results consistent with CRUNCH. Such data show that relative to younger adults, older adults overactivate at lower levels of task demand, where performance differences are minimal but underactivate at higher levels of task demand where there is a corresponding drop in performance (20,21). A recent report (22) has further demonstrated support for CRUNCH using multivoxel pattern analysis. Carp and colleagues (2010) used multivoxel pattern analysis to distinguish brain states associated with verbal versus spatial working memory processes and to assess whether these states could be distinguished with equal precision in younger and older adults. We found that for encoding and retrieval processes, which entail perceptual processing of the memory set and the probe item, respectively, older adults showed less distinct neural patterns compared with younger adults, consistent with age-related dedifferentiation (13). In contrast, during memory maintenance, when perceptual and response processes were minimal, distinctiveness varied due to memory load and age group: Older adults showed greater verbal and spatial distinctiveness at lower loads and decreased distinctiveness at high loads. Younger adults showed the opposite: lower distinctiveness at lower loads and increasing distinctiveness with increasing demand.

These results are important for two reasons. First, they demonstrate that evidence for potentially dysfunctional processes, like dedifferentiation, and for compensatory processes like CRUNCH in the same individuals. Thus both must be considered for a full account of neurocognitive aging. Second, the results indicate demand dependent age differences in recruitment of specific (distinct spatial vs verbal circuits) and general (nondistinct circuits), suggesting that both classes of neural resources may play a role in neurocognitive alterations with age.

Charles DeCarli: Dorsolateral Prefrontal Cortex Dysfunction Is Associated With White Matter Hyperintensity Volume

A number of cognitive and biological changes occur in the brains of healthy older adults. Behavioral studies of older adults reveal striking cognitive decline in measures of cognitive control (23,24). It has recently been suggested that specific impairments in goal maintenance may be the

hallmark deficit underlying these age-related differences (25). Goal maintenance, the ability to actively maintain goals in order to accomplish a task, is involved in many cognitive tasks and is thought to involve a network of regions dependent on the dorsolateral prefrontal cortex (26). Impairment in this network is consistent with hypotheses that attribute differences with cognitive aging to prefrontal cortex function (27,28).

Though age-related prefrontal dysfunction has been widely reported, the underlying mechanisms of this impairment remain poorly understood (27,28). White matter hyperintensities (WMH) increase in frequency with age and have been linked with a selective impairment of the frontal lobe structure and function across a wide range of studies (29–31). In a recent functional magnetic resonance imaging study, increasing WMH burden was associated with reduced prefrontal cortical activity during episodic memory retrieval and working memory (32). WMH burden was also associated with reduced activity in anterior cingulate cortex, a region functionally linked to the prefrontal cortex (32). The objective of this study (33) was to extend this previous work by investigating cerebrovascular disease as represented by WMH as a potential mechanism of age-related cognitive control deficits and prefrontal cortex dysfunction, possibly through altered connectivity of task-relevant cortical processing.

To test this hypothesis, older individuals with high WMH burden, older individuals with low WHM burden, and young adults were assessed in an event-related functional imaging scan while performing the AX-Continuous Performance Task.

Individuals with high WMH showed a significant reduction in dorsolateral prefrontal cortex activity during the high cognitive control cue condition relative to the low WMH group and young individuals (Figure 2). Conversely, those with high WMH showed greater activity in rostral anterior cingulate cortex compared with young individuals. These results are consistent with impaired cognitive control and a possible failure to deactivate default-mode regions in these subjects. Additionally, those with high WMH showed reduced functional connectivity between dorsolateral prefrontal cortex and task-relevant brain regions including middle frontal gyri and supramarginal gyrus relative to young and those with low WMH.

The functional imaging results of this study support the disconnection hypothesis of aging that suggests that injury to white matter tracts as manifest by WMH contributes to age-related alterations in prefrontal cortex function. Although inferential power is somewhat limited due to the small sample size, the functional connectivity results strengthen this argument by offering further evidence that WMH are associated with reduced correlations among nodes within brain networks activated during a cognitive control task. It is clear that cerebrovascular disease as manifest by WMH contributes to age-related changes in brain activation and connectivity, though not all age-related differences in our study were explained by WMH and other age-related effects in the brain are likely. A unique consequence of altered prefrontal function associated with severe WMH burden is the possibility that WMH may adversely affect the ability of the anterior cingulate to normally deactivate during evaluatory control or the modulation of task related systems activation and default network deactivation. It is therefore important to consider the role of cerebrovascular disease in age-related cognitive performance, given that it may be one of the underlying mechanisms of these changes and risk factors for cerebrovascular disease are modifiable.

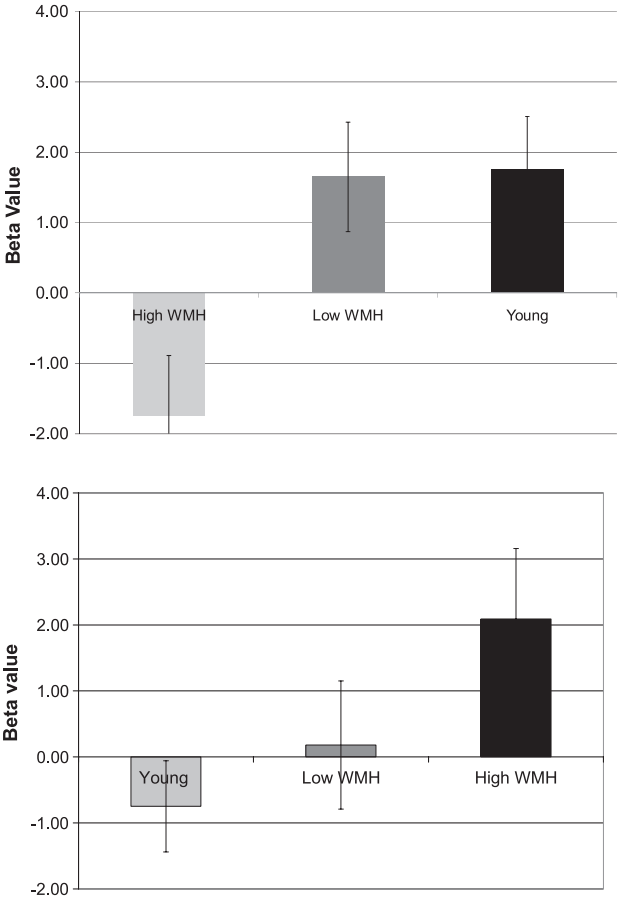

Figure 2. Group differences in activation patterns for Dorsal Lateral Prefrontal (top) and Anterior Cingulate Cortex (bottom). High white matter hyperintensities (WMH) differed significantly from Low WMH and Young groups under both conditions.

Reisa Sperling: Age and Amyloid-related Alterations in Memory Network Function

The ability to rapidly acquire and retrieve new episodic memories is thought to decline with advanced aging. Our work, as well as that of many other groups, has provided evidence of age-related, regionally specific, alterations in the brain networks supporting memory function. Our group has utilized a number of face-name associative memory paradigms to probe memory networks and to elucidate the changes in functional activity associated with age-related memory impairment. In particular, we have found that cog-

nitively normal older individuals primarily demonstrate functional alterations in the default network, especially the posteromedial cortices, during memory encoding (34). In contrast, we have repeatedly found that during successful encoding, cognitively normal older individuals engage the hippocampus and related regions in the medial temporal lobe to a similar degree as young subjects (34–36).

Recently, we have been probing the impact of amyloid-beta (Aβ) on memory network function, given the striking anatomic overlap between the default network and regional distribution of amyloid deposition seen on PET amyloid imaging (37,38). Converging evidence from PET studies, cerebrospinal fluid studies, and autopsy series suggests that approximately one third of clinically normal older individuals harbor fibrillar Aβ deposition, one of the hallmark pathologies of AD. Although it remains unknown whether clinically normal older individuals with high amyloid burden are in the "preclinical" stages of AD and will progress to manifest AD dementia, our recent studies suggest that amyloid deposition is associated with functional and structural changes that are similar to those observed in mild cognitive impairment and AD dementia patients (38–41). In particular, these studies have demonstrated evidence that much of the age-related alterations in default network function is attributable to the level of amyloid burden in these regions.

Finally, we have been investigating whether some of the decreases in memory performance previously attributed to "normal" aging, may in fact, be related to the presence of occult amyloid pathology. Our initial studies suggest that amyloid burden is related to neuropsychological test performance, even within the range of normal older individuals but that cognitive reserve plays a significant role in modulating the clinical expression of amyloid load (42). Thus, it is possible that studies of amyloid-positive older individuals include both individuals on the trajectory toward clinical AD and individuals who are uniquely able to withstand the potential effects of amyloid toxicity due to high brain and cognitive reserve. More sensitive episodic memory measures may be required to detect very subtle impairment related to early amyloid deposition (42).

In summary, our studies suggest that episodic memory is subserved by a distributed memory network and requires coordinated activity of both the default network and medial temporal lobe memory systems. Our studies during memory encoding processes suggest that age-related alterations are most evident in the default network, with preserved hippocampal function, but it is also likely that these networks interact with attentional systems that are also affected by the aging process. Our future functional imaging studies in cognitive aging will focus on the relationship between encoding and retrieval processes. As a substantial proportion of older subjects, classified as clinically normal, show evidence of amyloid deposition, it will be increasingly important to disambiguate the influence of early neurodegenerative disease from other age-related changes in the brain. Large longitudinal studies with more diverse cohorts will be required to fully elucidate the factors that predict cognitive decline in clinically normal older individuals and to better define the preclinical stages of AD.

Discussion

A variety of factors that impact neural networks and contribute to cognitive changes in aging have been proposed. A common theme is the importance of decline in executive functions with age and the importance of prefrontal cortex for these cognitive abilities. CRUNCH provides a framework for examining age-related changes in network activity and may offer an endophenotype for interventional studies. These task-related functional magnetic resonance imaging changes represent relative differences (not unilateral activation) across older adults of varying abilities, allow comparisons of older with younger adults, and provide a metric for mapping the relative extent of activations during specific tasks. It would be of great interest to further understand the underlying synaptic changes that underlie differences in activation patterns in older compared with younger subjects. For example, animal studies could help understand if age-related decrements in thin spines in dlPFC are associated with overactivation at lower task demands and underactivation at higher task demands in older compared with younger animals. Future functional magnetic resonance imaging studies are needed to establish their role in the compensatory processes suggested by CRUNCH.

The investigations of Drs. DeCarli and Sperling raise important questions about the effect of vascular damage and amyloid deposition in people who appear to be aging normally on tasks of memory and executive function. Understanding the effect of the aging vascular system on distributed neural networks is important because such damage is highly prevalent in older people, including those who are not destined to become demented and may play a role in age-related cognitive decline. So too is amyloid deposition a potential mediator of responses of neural networks and circuits to aging. Increasing data suggest that ischemia and amyloid deposition are linked through the "neurovascular unit"—the functional group of cerebrovascular cells, supporting glial tissue, and neurons (43). Although vascular damage associated with WMH results in breakdown of the blood–brain barrier (44), an intact blood–brain barrier is necessary for trafficking of Aβ across the endothelium, and ischemia may increase Aβ deposition through increased production and decreased vascular clearance (45,46). Conversely, Aβ is a potent vasoconstrictor and impairs cerebral autoregulation (43). Thus, vascular and neurodegenerative damage interact and are likely to affect cortical and cortical–subcortical networks. Such damage may be of particular importance to studies of age-related cognitive decline, as such damage likely alters the local field potentials that underlie the blood-oxygen-level–dependent changes measured with functional magnetic resonance imaging. The search for

preventive factors to ameliorate age-related cognitive decrements are needed, and several have been suggested here. Although targeting of the amyloid pathway has been of limited success to date, vascular disease is detectable and preventable and offers the possibility of early treatment. Finally, decline in physiologic processes due to aging, such as endocrine senescence, require further study and open new avenues for limiting age-related cognitive decline.

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