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CHAPTER 6

Brain plasticity and functional losses in the aged: scientific bases for a novel intervention

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Abstract: Aging is associated with progressive losses in function across multiple systems, including sensation, cognition, memory, motor control, and affect. The traditional view has been that functional decline in aging is unavoidable because it is a direct consequence of brain machinery wearing down over time. In recent years, an alternative perspective has emerged, which elaborates on this traditional view of age-related functional decline. This new viewpoint — based upon decades of research in neuroscience, experimental psychology, and other related fields — argues that as people age, brain plasticity processes with negative consequences begin to dominate brain functioning. Four core factors — reduced schedules of brain activity, noisy processing, weakened neuromodulatory control, and negative learning — interact to create a self-reinforcing downward spiral of degraded brain function in older adults. This downward spiral might begin from reduced brain activity due to behavioral change, from a loss in brain function driven by aging brain machinery, or more likely from both. In aggregate, these interrelated factors promote plastic changes in the brain that result in age-related functional decline. This new viewpoint on the root causes of functional decline immediately suggests a remedial approach. Studies of adult brain plasticity have shown that substantial improvement in function and/or recovery from losses in sensation, cognition, memory, motor control, and affect should be possible, using appropriately designed behavioral training paradigms. Driving brain plasticity with positive outcomes requires engaging older adults in demanding sensory, cognitive, and motor activities on an intensive basis, in a behavioral context designed to reengage and strengthen the neuromodulatory systems that control learning in adults, with the goal of increasing the fidelity, reliability, and power of cortical representations. Such a training program would serve a substantial unmet need in aging adults. Current treatments directed at age-related functional losses are limited in important ways. Pharmacological therapies can target only a limited number of the many changes believed to underlie functional decline. Behavioral approaches focus on teaching specific strategies to aid higher order cognitive functions, and do not usually aspire to fundamentally change brain function. A brain-plasticity-based training program would potentially be applicable to all aging adults with the promise of improving their operational capabilities. We have constructed such a brain-plasticity-based training program and conducted an initial randomized controlled pilot study to evaluate the feasibility of its use by older adults. A main objective of this initial study was to estimate the effect size on standardized neuropsychological measures of memory. We found that older adults could learn the training program quickly, and could use it entirely unsupervised for the majority of the time required. Pre- and posttesting documented a significant improvement in memory within the training group (effect size 0.41, $p<0.0005$), with no significant

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within-group changes in a time-matched computer using active control group, or in a no-contact control group. Thus, a brain-plasticity-based intervention targeting normal age-related cognitive decline may potentially offer benefit to a broad population of older adults.

Keywords: brain plasticity; cognitive rehabilitation; computer-based training

Introduction

This chapter reviews the scientific bases of a novel approach intended to improve the functional performance of older adults by slowing, halting, or reversing large-scale and progressive losses in brain functioning commonly experienced in later life. This hypothesis-driven approach is envisioned to be much like an exercise program for the brain that, ideally, should be initiated early in the aging process to enhance brain health and cognitive fitness before significant losses develop, but also could be effective later in the aging process when significant losses have already emerged.

The core of this chapter introduces a new perspective about the root causes of functional decline in aging that is based on decades of research on brain plasticity, experimental psychology, and other related fields. Brain plasticity refers to the lifelong capacity for physical and functional brain change enjoyed by humans and other animals and is inherently bidirectional: through the same mechanisms and plasticity processes, brain function can either be strengthened or degraded, depending on the circumstances. During normal aging, individuals typically undergo physical, behavioral, and environmental changes that, in the aggregate, promote negative plastic changes that degrade brain function. Four interrelated factors are proposed as the core causes of deterioration of functioning in older adults. These root causes of functional decline involve a complex interplay of physical brain deterioration, behavioral and environmental changes, and brain plasticity processes.

Just as brain plasticity processes with negative consequences can contribute to age-related functional decline, plasticity processes that strengthen brain function can provide a foundation for a therapy to restore sensory, cognitive, memory, motor, and affect systems in aging. This chapter focuses particularly on age-related cognitive decline, though the concepts and principles discussed here should apply to other areas of functioning (e.g., motor control) known to deteriorate with age.

The principles governing such brain plasticity processes are now sufficiently well understood to develop a new approach to maximize the quality and extend the duration of healthy aging. A brain-plasticity-based approach should be significantly more effective than current interventions for healthy aging, and could conceivably work in conjunction with a variety of other behavioral and pharmaceutical advances. When clinically validated, this science-based approach, which explicitly targets the underlying causes of long, slow functional decline, could signify a revolution in aging therapeutics.

Cognitive decline in aging is progressive and can become pathological

Cognitive decline is a universal aspect of the aging process. Memory decline during aging is pervasive (Park and Gutchess, 2003; Reuter-Lorenz and Sylvester, 2003; West, 2004). It may begin as early as age of 30 and, on the average, worsens slowly but steadily thereafter (Fig. 1) (Park et al., 1996). In addition, virtually all older adults will eventually develop a reduction in speed of processing (Salthouse, 1996). Various other cognitive abilities (e.g., visuospatial skill, executive functions, speech comprehension) have been found to commonly deteriorate with age (Harvey and Mohs, 2000; Zacks and Hasher, 2000; Schneider et al., 2002; Buckner, 2004). A number of labels have been used to describe normal age-related cognitive decline, including age-associated memory impairment, age-consistent memory impairment, benign senescent forgetfulness, late-life forgetfulness, and aging-associated cognitive decline (Ritchie et al., 2001; Bischkopf et al., 2002; Fillit et al., 2002). In

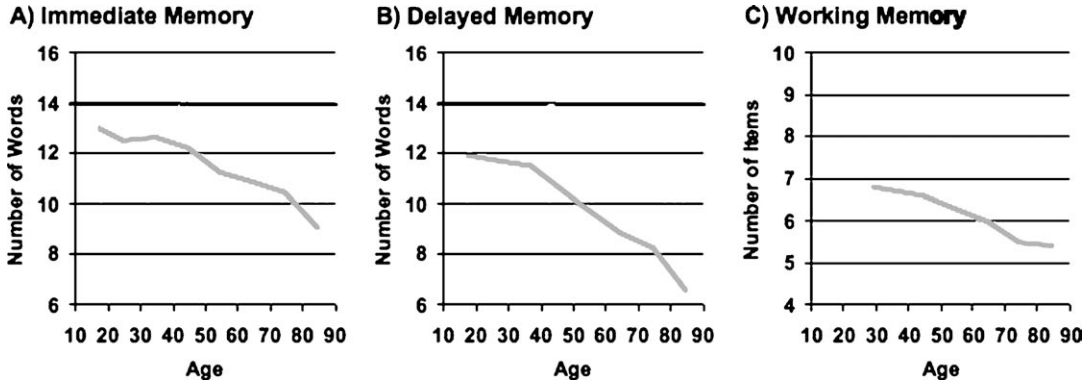

Fig. 1. Memory changes with age. Items recalled from a 16-word list in the immediate period (A, California verbal learning test CVLT-II trial 5) and in the delay period (B, CVLT-II delayed free recall), and number of digits recalled in a digit-span backwards task (C, Weschler memory scale III) (CVLT-II data courtesy of the University of California, San Francisco Memory and Aging Center).

normal aging, the extent of cognitive decline gradually increases with age, although there is considerable variability across individuals in the nature, degree, and timing of cognitive loss (Ylikoski et al., 1999; Park et al., 2003). Despite this variability, normal cognitive decline is an inevitable consequence of age; should individuals live long enough, virtually all will eventually lose a degree of cognitive efficacy.

Normal cognitive decline is distinct from pathological cognitive loss, which affects a sizeable proportion of older individuals and culminates in dementia. Pathological cognitive decline may look much like healthy aging in the beginning stages, but at some point a precipitous decrease in functioning, particularly in memory, typically occurs. About one in four older adults will experience a decline now generally diagnosed as mild cognitive impairment (MCI), in which function in a specific cognitive domain (e.g., memory) is impaired while activities of daily living generally remain intact (Unverzagt et al., 2001). Individuals with MCI show extreme losses in neuromodulatory activity crucial for sustaining learning operations and vivifying memory (AsDEaRC, 2001–2002, 2002).

MCI may be a transitional or high-risk state between normal cognition and dementia, as 80% of individuals diagnosed with MCI are diagnosed with dementia within 5–8 years (Craft et al., 2003). In contrast, only 1−2% of adults with normal age-related cognitive decline develop dementia each year (Craft et al., 2003).

Some argue that if adults were to live long enough, the progressive physical deterioration of the brain would eventually cause dementia in all cases (Terry and Katzman, 2001). Others argue that cases of dementia (and perhaps MCI) are specific pathological conditions that are not the expected end states of healthy aging (Fillit et al., 2002). Data exist to support both theories regarding the inevitability of dementia. On one hand, older adults become more vulnerable to developing dementia with increasing age, such that almost half of the adults of age 85 and above have Alzheimer's disease (AD) (National Institute on Aging, 1998). On the other hand, many individuals remain cognitively vital even into extreme old age, evidencing only minor changes in speed of processing and the most attention-demanding tasks (Fillit et al., 2002). In either case, it is clear that normal cognitive decline is a universal phenomenon, and that a clinically significant amount of cognitive decline is increasingly common with age.

Root causes of age-related cognitive decline

Changes in the brain occur with aging

Thousands of studies have documented the physical, anatomical, physiological, and chemical changes that occur in the brain with aging (Bussiere and Hof, 2000; Magistretti et al., 2000; Raz, 2000; Mattson, 2003; Backman and Farde, 2005).

In aggregate, this large body of research has established five fundamental principles: (1) neurons and the strengths and richness of their interconnections progressively atrophy as individuals age; (2) the deteriorating brain machinery includes cortical areas and subcortical nuclei that are specifically related to sensation, cognition, memory, motor control, and affect; (3) the metabolic decline and down-regulation of key neuronal populations commonly precede cell death; (4) many aspects of physical and chemical deterioration and emergent neuropathology are correlated with general and specific behavioral losses; and (5) although there is substantial variability in the time of onset, course, and magnitude of functional and physical deterioration, these changes are a virtually universal outcome of the later years of an extended human life.

The above observations have led to a viewpoint that is often termed the "wear and tear" hypothesis of cognitive decline in aging (Aldwin and Gilmer, 2004). This hypothesis suggested that brain machinery simply wears down over time. The observed anatomical changes (e.g., cell death, metabolic status, connectivity) and consequent functional changes (e.g., memory deficits, reduced processing speed, impaired spatial abilities) are the consequences of any biological or mechanical machine that has been in operation for multiple decades. The natural conclusion of the wear and tear hypothesis is that cognitive decline is normal, inevitable, and irreversible (Baron and Cerella, 1993).

The physical aging of the brain obviously plays an important role in age-related cognitive decline. However, it is increasingly clear that the inevitable physical deterioration of the aging brain cannot completely account for many of the changes in functioning observed in older adults. The extensive literatures on brain plasticity and the perceptual psychophysics of aging strongly suggest that brain plasticity with negative consequences is a crucial contributor to age-related cognitive decline. As individuals age, their schedules and strengths of brain engagement substantially change, and are paralleled by active degradation of brain function. It is believed that such changes in brain use and engagement are direct and critical contributors to age-related cognitive decline.

Learning changes the brain through brain plasticity

Brain plasticity refers to the brain's lifelong capacity for physical and functional change; it is this capacity that explains how experience induces learning throughout life. The concept of brain plasticity is more than a century old (Woodruff-Pak, 1993), and its study has been ongoing for several decades. Historically, brain plasticity has been more often discussed in the contexts of early child development, stroke recovery, and perceptual learning than in regard to aging.

Before the concept of lifelong brain plasticity was introduced, many researchers believed that the human brain was hard-wired in early life (Woodruff-Pak, 1993). Evidence supported this view by demonstrating that the brain developed the physical structures and long-range interconnections that determine neurological functioning during an early "critical period" of child development. It was established that, during this critical period, the brain was capable of substantial remodeling in response to alterations in input; but after the critical period closed, it was generally observed that the brain was not capable of further significant remodeling, elaboration, or growth. This notion that the brain developed its immutable long-range interconnections in early life contributed to the belief that age-related cognitive decline was inevitable and irreversible (Baron and Cerella, 1993).

Today, after decades of accumulated cross-disciplinary research, a new and very different view has emerged about the origin and maintenance of human abilities. This view holds that the brain is plastic; that is, the brain is capable of reorganization, including developing new short-range interconnections, at any age throughout adult life.

Brain plasticity experiments have documented a number of important ways in which progressive learning changes brain machinery. In aggregate, this research demonstrates that the adult brain continuously adapts to disproportionately represent relevant sensory stimuli and behavioral outputs with well-coordinated populations of neurons. This is achieved by engaging competitive processes in brain networks that refine the selective representations of sensory inputs or motor actions, typically resulting in increased strengths of cortical resources devoted

to, and enhanced representational fidelity (or "precision") of, the learned stimulus or behavior.

Brain plasticity with positive consequences

Competitive processes underlie all brain plasticity. In perceptual, cognitive, and motor skill learning tasks, competitive processes result in the narrowing of time and space constants that define the selectivity of processing in cortical networks. In this way, the selective responses of cortical neurons specialize to meet the specific demands of the task. The representation of input timing is dramatically elaborated, and the cortex's ability to respond accurately in fast, precisely measured time as a receiver and a controller of action are dramatically advanced. For example, in monkeys trained to detect a specific pattern of stimulation to the fingers, the somatosensory cortex reorganizes to represent that specific input pattern with large, well-organized, and spatiotemporally coherent responses (Recanzone et al., 1992a, b; Wang et al., 1995). Similarly, in monkeys trained to perform demanding motor tasks (e.g., retrieving food pellets, turning bolts), the primary motor cortex reorganizes to represent the specific required motions of the digits and hand with larger cortical areas (Nudo et al., 1996). These types of changes have now been well documented in humans as well; for example, violin players have been shown to have stronger and more distinct representations of the fingers in the right hemisphere, corresponding to the individuated finger movements required by their left hands (Elbert et al., 1995). This example illustrates that beautifully elaborated and highly differentiated cortical representations develop in the learning of any highly skilled behavior.

In learning skilled behaviors, such as playing a musical instrument, as brain machinery is progressively refined in its specificity, selectivity, and fidelity through competitive processes, it increases the representational power of behaviorally important sensory stimuli and motor outputs, as manifested by increased response magnitude and distributed response coherence. This is achieved, in large part, by plasticity processes that increase cortico–cortical connectional strengths between neurons in nearly simultaneously excited cortical networks.

A key effect of this learning-induced change is to strengthen the signal-to-noise ratio of relevant cortical activity. Cortical systems operate against a constant background of internal noise from high spontaneous network activity levels; detecting the signal in this noise is a key challenge to such systems. Enhancement of the signal-to-noise ratio is likely to be a key mechanism by which learning improves brain function.

The outcome of these competitive processes is positive because, through the locally adaptive processes by which the brain specializes to represent salient input, the brain's processing machinery becomes more locally and globally adapted to perform important behavioral tasks. As a general principle, brain plasticity with positive consequences is likely to underlie virtually all forms of perceptual and skill learning in the brain.

Brain plasticity with negative consequences

We have just described how brain plasticity underlies all learning (e.g., perceptual, cognitive, motor). Because plasticity processes are inherently competitive, there always will be a competitive "winner" and "loser" (i.e., excitatory and inhibitory synaptic changes); thus, plastic changes with negative consequences are just as common as those with positive outcomes. Plasticity can be manipulated by adjusting the learning context; it is possible to actively degrade and weaken the brain processing machinery just as easily as it is possible to refine, elaborate, and strengthen the processing machinery.

One example of plasticity with negative consequences is seen in monkeys trained under conditions in which heavy synchronous input is delivered across fingers (Jenkins et al., 1990; Allard et al., 1991; Wang et al., 1995) or the entire hand (Byl et al., 1996). In response to this type of sensory stimulation, the somatosensory cortex reorganizes to adaptively represent the undifferentiated spatiotemporal characteristics of the trained input. This results in an undifferentiated map — with abnormally large, overlapping receptive fields and degraded spatial and temporal response characteristics. While this map is adaptive in that it represents the use conditions of the hand, it is maladaptive in that the map does not support the

use of the hand under conditions that require the accurate processing of sensory inputs and motor outputs with high degrees of spatiotemporal complexity.

Although this example shows how negative plastic changes can be actively induced, these changes more often occur naturally (i.e., without conscious effort) in later life. For example, as people age they commonly begin to stereotype and simplify behaviors that previously were quite complex and elaborated. The brain is likely to automatically adjust to these less complex behaviors by simplifying its representations that support them.

We refer to these changes as brain plasticity with negative consequences because, through the locally adaptive processes by which the brain specializes to represent salient input, the brain's processing machinery becomes less locally and globally adapted to perform important behavioral tasks. Brain plasticity with negative consequences is very likely to underlie specific pathological conditions (e.g., focal dystonia of the hand) (Byl et al., 1996) as well as general sensory or cognitive dysfunctions (e.g., learning impairments in children) (Tallal et al., 1996a). Based on a growing literature in the fields of psychophysics, neurology, neuropsychology, and brain plasticity, it is almost certain that the problems of age-related cognitive decline are substantially caused by negative dimensions of brain plasticity as well.

Age-related cognitive decline is a problem of brain plasticity with negative consequences

Our forebrain processing machinery is sustained in a refined, powerful, and efficient operational state by its intensive use under challenging conditions. In adulthood, continuous active interaction with environments that are demanding to sensory, cognitive, and motor systems is necessary to maintain brain health and cognitive fitness. As people age, a self-reinforcing, downwards spiral of reduced interaction with challenging environments and reduced brain health significantly contributes to cognitive decline (see Table 1). This downward spiral might begin either from a reduction in the schedule and engagement of brain activity or from an initial small loss in brain function driven by degraded sensory inputs (or, more likely, from both). In either case, once such a spiral begins, it continues through a sequence of interrelated events that reinforces a cascade of negative interactions, resulting in worsened cognitive fitness and brain health. We identify four interrelated factors as central and mutually reinforcing:

1. reduced schedules of activity
2. noisy processing
3. weakened neuromodulatory control
4. negative learning

Reduced schedules of activity

As people age, they typically change their activity patterns, such that the level of engagement in cognitively demanding activities is lessened (Hultsch et al., 1999). Even people with historically high levels of cognitive activity typically reduce their level of stimulation, either by conscious choice (e.g., retirement) or by unconsciously "resting on their laurels" and pursuing only activities at which they already excel. This results in less overall

Table 1. Root causes of functional decline in aging

Reduced Schedules of Activity – Reduction in the schedules of inputs and actions that engage the brain that are required to continuously refine existing skills and drive new learning. Often referred to as "brain disuse."
Noisy Processing – Brain processing that produces low-fidelity, unreliable, and weakly-salient cortical representations of sensory inputs and actions. This occurs because the deteriorated brain produces poor signal quality, and must adjust its time and space constants to process these degraded signals, thus creating a noisy processing machine.
Weakened Neuromodulatory Control – Down-regulation of metabolism and connectivity of neuromodulatory control systems caused by age-related physical deterioration and reduced schedules of activity.
Negative Learning – Changes in behavior that accelerate cognitive decline, typically chosen because ordinary behaviors have become more difficult.

stimulation for sensory, cognitive, and motor systems, and importantly reduces stimulation for attention, reward, and novelty-detecting neuromodulatory systems. Through animal models, scientists have shown that the physical and functional consequences of brain disuse (engendered by exposing animals to impoverished environments) parallel the signature changes in the aged human brain. These studies have documented that a lack of brain engagement causes negative changes in neuronal metabolism (e.g., the production and function of neurotransmitters, receptors, and other key functional biochemical constituents of neurons), and in neuronal architecture (e.g., the elaboration of dendrites, axonal arbors, spines and synapses, cortical and subcortical neuropil, and gray matter) (Diamond et al., 1975; Katz and Davies, 1984; Sirevaag and Greenough, 1985; Beaulieu and Colonnier, 1989; Park et al., 1992; Melendez et al., 2004). These negative physical changes are accompanied by impaired learning and memory capacities that are thought to be the result of long-term alterations in neuronal plasticity driven by exposure to impoverished, nonstimulating, and noncomplex environments (Lewis, 2004). The parallels between the physical and functional changes seen in these models of brain disuse and those seen in the aged human brain are unmistakable, and the fact that such changes are reversible through environmental enrichment (Winocur, 1998) suggests that age-related cognitive decline may be slowed, arrested, or even reversed.

Noisy processing

Another consequence of aging is that sensory input from all systems (e.g., auditory, visual, tactile, proprioceptive) is degraded as a result of basic deterioration of peripheral sensory organs (e.g., loss of hair cells in the cochlea, loss of photoreceptors in the retina, changes in skin properties). The brain must adjust to these degraded sensory inputs by lengthening space and time integration constants in an effort to detect relevant signals. These adaptive changes are made at a cost — brain systems with long space and time integration constants cannot accurately represent the details of spatiotemporally complex signals. This inaccuracy manifests as temporally and spatially noisy responses to relevant stimuli. These adaptive changes necessarily slow the speed of information processing as well.

Weakened neuromodulatory control

A further consequence of aging is that the metabolism, connectivity, and eventually, structure of neuromodulatory control systems, which regulate learning and plasticity in adults, become degraded. The key neuromodulators controlling plasticity are ACh (Bartus et al., 1982), which modulates synaptic plasticity in the hippocampus, cerebral cortex, and striatum (Doya, 2002), and controls memory and the rate of learning (Gu, 2002); dopamine, which mediates many aspects of cognitive, emotive, and motor functions (Gu, 2002), and is implicated in the prediction of reward and in action learning (Doya, 2002); serotonin, which regulates the time scale of reward prediction (Doya, 2002); and norepinephrine, which controls mental alertness and attentional focus (Usher et al., 1999). In aggregate, degraded neuromodulatory control systems weaken the brain's control over its own plasticity, lowering learning rates and trapping the brain in potentially inappropriate or unhelpful patterns of activation.

Negative learning

As reduced schedules of activity, noisy processing, and weakened neuromodulatory control interact to make novel or demanding activities more challenging to perform, individuals naturally adapt their behaviors in ways that can reinforce negative aspects of the sensory input and motor output. For example, as it becomes harder to follow the rapid speech of a child on the telephone, an older adult might turn up the volume on the phone (increasing signal distortion along with loudness), find it more frustrating to have such conversations (decreasing neuromodulatory responses required to maintain high brain function), or simply choose to have fewer of such conversations (further reducing the schedule of brain activity).

Substantial reorganizations in the responses of older brains to sensory and cognitive tasks relative

to younger brains have been measured using functional magnetic resonance imaging (fMRI). In a variety of such tasks, the changes seen in older brains can be interpreted as a dedifferentiation of response properties, including the recruitment of contralateral or new brain regions or the substitution of different brain regions to support task performance (Park et al., 2001). This neurological dedifferentiation is most likely a manifestation of the physiological brain plasticity with negative consequences we describe here.

In aggregate, these four factors create a brain that is substantially less capable of representing the spatiotemporal detail of incoming stimuli, less able to represent such stimuli with strong, coherent, and salient neural activity, less able to actively modulate its own activity and capacity for change, and less able to support rapid interactions across relevant brain systems. Such a brain will manifest longer time and space constants, a slower processing speed, and integrated sensory, cognitive, and motor dysfunction. Below, we review the data from a wealth of psychophysical, neuropsychological, and cognitive studies that demonstrate that aged brains manifest reduced accuracy and speed of information processing as well as integrated dysfunction.

Cognitive decline is driven by changes across brain systems

Although sensory and cognitive systems are often discussed and studied as separate entities, a large body of anatomical, physiological, and behavioral evidence suggests that, in fact, these systems are very tightly interrelated (Schneider and Pichora-Fuller, 2000). Information continuously flows both forward and backward through the brain's sensory, cognitive, and motor systems. Sensory systems detect and analyze fundamental stimulus properties and feed this information forward to cognitive systems that store, manipulate, and act on it. Cognitive systems feedback to influence sensory processing through attention, expectation, memory, and context, while directly driving motor systems to execute planned activities. Motor systems are tightly integrated with cognitive systems through premotor areas involved in movement planning, and indirectly provide feedback to sensory systems through proprioceptive and vestibular systems. Because sensory, cognitive, and motor systems are parts of a highly integrated information processing system, disruption in any one system would be expected to cause disruption in the others, and degrade the overall accuracy and speed of information processing (Schneider and Pichora-Fuller, 2000). Indeed, deficits in sensory, cognitive, and motor functioning are common in older adults (Harvey and Mohs, 2000). Although this chapter focuses on sensory and cognitive deficits, the principles and science underlying these issues are also directly relevant to motor function in older adults.

Researchers have begun to explicate the complex ways in which these systems interact. It is now clear that sensory systems with degraded function negatively affect cognitive function. The source of such degraded sensory input has typically been assumed to be in the periphery (e.g., loss of hair cells in the cochlea, loss of photoreceptors in the retina) given the well-documented changes that occur there (Scialfa, 2002; Madden et al., 2003). However, a growing literature has shown that central sensory processing deficits play a significant role in the reduced cognitive performance of older adults as well (Schneider and Pichora-Fuller, 2000; Faubert, 2002). In the auditory system of older adults, the negative effect of sensory losses on cognitive performance has been extensively documented. Similar findings are emerging in the study of the visual system. Other systems (e.g., somatosensory, vestibular) also decline with age, although their relationship to associated cognitive systems is not yet well understood. Below, we summarize the deficits in the auditory and visual systems, and the research that explores how these deficits contribute to cognitive decline in older adults.

Changes in the central auditory system contribute to cognitive deficits in aging

Many adults experience a decline in auditory sensitivity with age, called presbycusia, which is commonly experienced as a sensory loss in the high-frequency range of hearing, and is caused by the deterioration of inner hair cells in the cochlea. However, many other age-related auditory sensory

deficits have been shown to exist independent of, or in combination with, high-frequency hearing loss, suggesting that these deficits cannot be solely attributed to deterioration of the peripheral sensory system and must be rooted in the central auditory system (Schneider and Pichora-Fuller, 2000).

The ability to temporally resolve an auditory signal is critical for accurate speech perception (Drullman, 1995a, b) and decreases with age (Abel et al., 1990; Moore and Peters, 1992; Fitzgibbons and Gordon-Salant, 1994; Schneider et al., 1994). By comparing the temporal resolution abilities of young adults with good hearing, hearing-impaired older listeners, and older listeners with good hearing, researchers have determined the extent to which hearing loss and age may mediate temporal resolution. These studies consistently have shown that older adults with good hearing have reduced temporal resolution compared to younger adults with good hearing (i.e., temporal resolution declines with age), and that there is no difference in temporal resolution abilities of older listeners with good hearing and those with hearing loss (i.e., reduced temporal resolution in older adults is unrelated to hearing loss) (Abel et al., 1990; Moore and Peters, 1992; Fitzgibbons and Gordon-Salant, 1994; Schneider et al., 1994).

Older adults also experience challenges with speech perception. A common complaint among older individuals is that everyday conversations are hard to understand — speakers seem to mumble or speak too fast, and cannot be understood in noisy situations (Schneider et al., 2002). Even when adults with good hearing sensitivity are in quiet conditions, they may not fully understand all words or speech sounds (Schneider et al., 2002). Consistent with this subjective loss of cognitive efficacy, experimental studies have shown that older adults make more errors than younger adults in recognizing and remembering fast speech (Pichora-Fuller et al., 1995; Wingfield et al., 1999; Schneider et al., 2002), speech under noisy conditions (Humes and Roberts, 1990; Humes and Christopherson, 1991; Murphy et al., 2000), and speech lacking contextual cues (Gordon-Salant and Fitzgibbons, 2001). Moreover, these deficits are apparent even when controlling for hearing loss (Dubno et al., 1984; Cheesman et al., 1995; Gordon-Salant and Fitzgibbons, 2001; Gordon-Salant and Fitzgibbons, 1993), suggesting that peripheral sensory loss is not the only factor in this aging deficit.

Although the neurological origins of these deficits in speech perception are not yet well understood, significant insights have been gained from studies comparing younger and older adults. In studies of speech rate and background noise on speech recognition in older and younger adults, the performance of younger adults when listening to rapid (Wingfield and Lindfield, 1995; Wingfield, 1996) or noisy (Schneider et al., 2002) speech was similar to that of older adults listening to slower speech or speech under quiet conditions. These results suggest that the neurological dysfunctions in older adults act to lower the temporal fidelity of and add noise to auditory input.

These and other studies have gone on to demonstrate that these perceptual deficits have deleterious consequences for memory and cognitive performance in older adults. Several studies of the role of noise in speech processing have shown that when young adults performed verbal memory tasks under signal-to-noise conditions that matched their sensory performance to the relatively poor performance of older adults, their memory abilities were equivalent to those of older adults (Murphy et al., 2000; Schneider et al., 2002). These results demonstrate that the poor sensory function of older adults can significantly impair their memory for speech.

In aggregate, there is a large and increasingly deep body of knowledge from studies of auditory psychophysics, perception, and cognition in older individuals, which argues that degraded representational fidelity and noise in the central auditory system is responsible for crucial auditory processing deficits seen in older adults, and that these sensory processing deficits can in turn cause meaningful deficits in memory and cognitive functions (Schneider and Pichora-Fuller, 2000). The logical implication of this literature and the literature of brain plasticity is that a training program designed to improve the fidelity of the representation of auditory stimuli in older adults should lead to substantially improved cognitive and memory performance in tasks involving the auditory system.

This conclusion is not in conflict with studies that have shown that peripheral sensory loss also contributes to cognitive deficits in older adults. However, we contend that central processing deficits could be remediated with a plasticity-based training program while there is no known remedy for peripheral sensory loss.

Changes in the central visual system contribute to cognitive deficits in aging

Age-related changes in the eye, whether caused by specific pathologies (e.g., cataracts, glaucoma, macular degeneration) or generalized issues in aging (e.g., decline in the number of rods), can reduce visual acuity, contrast sensitivity, color vision, and light sensitivity. This decline in the visual peripheral sensory system without question contributes to a less accurate and more noisy representation of the visual world in older adults. However, as in the auditory system, there is a growing body of evidence that shows that the decline in various basic visual abilities occurring with age is independent of optical factors (Morrison and McGrath, 1985; Owsley et al., 1985; Nameda et al., 1989), suggesting that a deteriorated central visual sensory system produces a noisy representation of the visual world that substantially contributes to a decline in visual cognitive processing (Schneider and Pichora-Fuller, 2000).

Impairments in central visual perception include a difficulty in detecting and discriminating between static peripheral targets; problems with motion perception; an impaired ability to track and visually process moving objects (Sharpe and Sylvester, 1978; Scialfa and Kline, 1988; Kline, 1994; Olincy et al., 1997), difficulty in identifying and discriminating letters (Akutsu et al., 1991), trouble inferring three-dimensional structure from two-dimensional images (Plude et al., 1986; Robins-Wahlin et al., 1993), and difficulty in mental rotation (Dollinger, 1995); and poorer face discrimination abilities (Owsley et al., 1981; Eslinger and Benton, 1983; Koss et al., 1991; Cronin-Golomb et al., 2000). Older adults show deficits in backward masking tasks involving visual stimuli (Kline and Birren, 1975; Kline and Szafran, 1975; Walsh, 1976) and in flicker fusion tasks (Kim and Mayer, 1994), both of which suggest abnormalities in temporal integration. They are also less sensitive to object movement (Elliot et al., 1989; Kline et al., 1994), and are less able to detect coherent motion (Trick and Silverman, 1991; Wojciechowski et al., 1995). In combination, these spatial and temporal psychophysical deficits suggest that problems in the central visual system substantially impair even the earliest stages of visual processing in older observers.

As in the auditory system, a growing number of studies suggest that age-related problems in visual cognition, visual memory, and visuospatial skills can be traced to degraded central visual system processing. Lowering the contrast of stimuli in visual neuropsychological tasks to mimic the contrast deficit of older adults decreases the cognitive performance of younger adults to that of a typical 50–55-year-old (Spinks et al., 1996). Improving the contrast of stimuli significantly increases the performance of older adults in reading comprehension (Echt and Pollack, 1998). When noise is added to visual stimuli to mimic the poor discrimination abilities of older participants, the ability of younger participants to identify visually presented words declines, such that it can no longer be distinguished from the performance of older adults (Speranza et al., 2000).

Although this literature is less well developed than research in the auditory system, these findings argue that degraded representational fidelity and noise in the central visual system are responsible for crucial visual processing deficits seen in older adults, and that these sensory processing deficits can in turn cause meaningful deficits in memory and cognitive functions. Together, these literatures suggest that degraded representational fidelity and consequent cognitive and memory deficits are general operating principles of the aging brain, and that training programs targeting each sensory system in turn should lead to substantially improved cognitive and memory performance.

Physical and functional deterioration in the brain can be slowed, arrested, and reversed

As already mentioned, there now exists ample scientific support for the idea that the brain has a lifelong capacity for plasticity. We have just

described how reduced schedules of activity, noisy processing, weakened neuromodulatory control, and negative learning work in concert to significantly impair cognition in older adults. If these conditions were reversed, would it be possible to restore cognitive functioning in older adults that had experienced significant decline? Evidence from human and animal research strongly indicates that substantial physical, sensory, cognitive, and motor recovery is possible.

Human studies have documented that cognitive activity wards off future decline with aging, perhaps by building what others refer to as a "cognitive reserve," which may be a euphemism for strengthened brain processing machinery (Whalley et al., 2004). In the past few years, various well-designed, prospective studies have shown that participation in cognitively stimulating activities (Wilson et al., 2002, 2003), intellectually complex work (Schooler et al., 1999), and leisure activities (Scarmeas et al., 2001; Verghese et al., 2003) during adulthood reduces the risk of loss of cognitive abilities in later life. Involvement in cognitive activity would clearly counter each of the four conditions believed to contribute to functional decline in the aged: cognitive activity is the opposite of brain disuse; it would strengthen the brain processing machinery to ensure less noisy processing; it is likely to be done in behavioral contexts (e.g., attention, reward, novelty) that strengthen neuromodulatory control; and it disrupts the downwards spiral of negative learning.

Human behavioral studies have shown that losses in sensory, cognitive, and motor processing can be reversed. Specific training can refine degraded representations in the sensory and motor cortices (Bao et al., 2003; Byl et al., 2003), improve signal-to-noise conditions for neuronal representations and distributed neuronal response coherence (Deutsch et al., 2000; Nagarajan et al., 2000; Nagarajan and Merzenich, unpublished manuscript), and restore the effectiveness of long-range feed-forward connections (Temple et al., 2000, 2003; Olesen et al., 2004). Neglected cognitive skills can be strengthened and refined by use (Wolf et al., 2001; Dick et al., 2003).

A large and growing body of animal studies have shown that an enriched environment designed to be cognitively stimulating promotes positive plastic changes in the brain and can reverse the negative physical, sensory, and cognitive aspects of aging. (For reviews, see Diamond, 2001; Mohammed et al., 2002; Lewis, 2004; Li and Tang, 2005). These studies have shown that new neuron production can be increased in areas where cell division and proliferation are possible (e.g., the hippocampus) (Kempermann et al., 1997, 2002; Lemaire et al., 1999) and apoptotic cell death can be reduced (Young et al., 1999). Gray matter can be thickened: dendrites, spines, and synapses in the cortical neuropil can be elaborated (Diamond et al., 1975; Greenough et al., 1978, 1985; Floeter and Greenough, 1979; Green et al., 1983; Diamond et al., 1985; Mohammed et al., 1993; Rosenzweig and Bennett, 1996; Mattson et al., 2001; Kleim et al., 2002; Mohammed et al., 2002; Frick and Fernandez, 2003; Frick et al., 2003). Even myelination, which had previously been thought to be irrecoverable in the adult brain, can probably be restored (Stevens et al., 2002; Saleh et al., 2003; Piraino et al., 2005).

Neuromodulatory control systems, weakened during aging, can be strengthened by behavioral training. Such training can up-regulate the metabolic states and the production and release of key neurotransmitters of limbic system and basal ganglion neurons (Nakamura, 1991; Bezard et al., 2003; Cohen et al., 2003; Tillerson et al., 2003). Through their more effective and intense reactivation, cortical and subcortical terminals of modulatory control nuclei can be elaborated (Wolfman et al., 1994; Spengler et al., 1995). Under optimal environmental conditions, almost every physical aspect of the brain can recover from age-related losses. A degradation of vascular dynamics attributable to ACh control of nitric-oxide-related enzymes believed to presage AD pathology may be at least partially overcome (Hilbig et al., 2002). A recent study demonstrated that even certain pathological hallmarks of AD (e.g., amyloid bodies) could be ameliorated by exposure to an enriched environment (Lazarov et al., 2005).

Numerous studies have shown that behavioral training or exposure to a novel environment can refine representations in the sensory, somatosensory, and motor cortices of animals (Wang et al.,

1995; Nudo et al., 1996; Xerri et al., 1996, 1998; Byl et al., 1997; Coq and Xerri, 2001; Nudo et al., 2003). In addition, exposure to an enriched environment can improve memory and learning in older animals (Doty, 1972; Cummins et al., 1973; Berman et al., 1988; Kobayashi et al., 2002; Frick and Fernandez, 2003; Frick et al., 2003; Fernandez et al., 2004), and those that are cognitively impaired (Rampon et al., 2000; Arendash et al., 2004) perhaps by inducing synaptic structural changes that enhance memory and learning (Kempermann et al., 1997; Rampon et al., 2000). The negative effects of earlier exposure to an impoverished environment can be at least partially reversed by exposure to an enriched environment later in life (Winocur, 1998).

This very large group of studies shows that substantial recovery is possible in the aging brain: physical losses can be reversed, and many aspects of sensory, motor, neuromodulatory, and cognitive systems can be restored to optimal levels of functioning. Additional experimental and applied studies conducted over the next several decades will more clearly define the extent of positive plastic changes that may be achieved, and the conditions under which these changes can be maintained over time.

For brevity's sake, we have selected four examples of brain plasticity research for more in-depth discussion. In each example, we describe how negative plasticity processes degrades sensory, cognitive, or motor functioning and how positive plasticity has restored behavioral and neurological functioning.

Age-related decline in rat

Negative plasticity in elderly rat

As a rat nears the end of its life, it loses control of its forepaws. This loss is manifested, for example, by increasing functional difficulty in food object retrieval and manipulation. Across the same period of time, the rat's mobility becomes progressively degraded: its gait becomes slow and clumsy. If the rat lives long enough, it will lose the ability to control its hind legs in locomotion; turn its feet over so that their hairy dorsal surface is touching the cage surface (apparently because contact of the glabrous surface with the ground is painful); and drag itself around its environment using its forelegs. The aged rat's difficulty in feeding itself contributes to the rat's death shortly into its third year of life.

The neuronal basis of the rat's loss of control of its paws and limbs is revealed through reconstructing the cortical maps of the rat's paw surfaces in the somatosensory cortex and movement representations in the motor cortex (Godde et al., 2002). The cortical maps of the paw surfaces and movement representations are profoundly dedifferentiated and noisy in the old rat, with cortical neurons responding weakly and unreliably (Coq and Xerri, 2000; Godde et al., 2002). In such a cortex, inputs have weak salience and poorly engage nondeclarative memory processes crucial for sustaining complex, normal forepaw grasp behaviors.

In the 2-year-old rat, physical signs of deterioration are broadly expressed in the somatosensory and motor cortices, and in subcortical thalamic and limbic system nuclei (Godde et al., 2002). The rat's gray matter is thin; the neuropil is shrunken; neurons have less complex dendrites and fewer spines; synapses are less elaborate; intracortical axons are less complexly branched; and myelination is reduced. In sum, the cerebral cortex, and the subcortical thalamic and modulatory control nuclei that support it, are slowly dying. This deterioration in the cortex and the modulatory subcortical nuclei is paralleled by slower learning rates and lower learning ceilings in aged animals. A degradation of dynamic control of vascular perfusion almost certainly is due to the inexorable degradation of modulatory control system (nucleus basalis, locus coeruleus) function.

Positive plasticity-based training reverses age-related decline

Many of these destructive functional and physical changes in the aged rat can be reversed through appropriate, targeted, intensive retraining of the rat's forepaws, and postural and mobility control (Churs et al., 1996; Reinke and Dinse, 1999). The

training that was applied in this model engages the rat in behaviors that progressively reestablish refined representations of the paw surfaces and of paw and limb movements. Rats were trained to cross-rotating bumpy rods to retrieve a food reward. The difficulty of the task was progressively increased by narrowing the bar and increasing the rate of rotation. Successfully crossing the bar delivers significant spatiotemporally complex input to the somatosensory system while demanding substantial attentional resources and requiring complex motor output.

Following training, the reversal of these physical changes is revealed by the restoration of relatively normal forepaw maps in the primary somatosensory and motor cortices. The restoration of the cortical maps in these rats translated into functional recovery: trained rats recovered their ability to manipulate food objects with their forepaws and control their limbs in locomotion. With these functions restored, the rats lived 4–5 months longer than would otherwise be the case.

Although the documentation of physical changes following such training is still incomplete, the limited studies conducted to date and other related experiments show that the cortical gray matter can be thickened, largely through an increase of neuropil; dendrites can be elaborated; the resting metabolism of cortical and subcortical areas can be increased; the reversal of the loss of dynamic brain perfusion and the up-regulation of a nitric-oxide-related enzyme indicates that ACh production and nucleus basalis function becomes more normal.

This model shows that appropriately structured and intensive behavioral engagement can substantially reverse both physical and functional deterioration of complex forebrain-mediated behaviors in older animals. While the changes induced in these experiments do not completely physically or functionally restore youthful behaviors, the positive, normalizing changes that do occur are expressed on a very large scale. Moreover, the scope of the training employed in these experiments has been very limited. More intensive and elaborate training should produce considerably more powerful and complete reversals of functional and physical losses.

Remediation of acquired hand movement disorders

Negative plasticity in overtrained humans and monkeys

Acquired hand movement disorders (e.g., focal hand dystonia) often arise from specific forms of occupational hand use in humans (e.g., playing the piano, keyboard data entry). We have induced acquired movement disorders in monkeys through a negative plasticity scenario, and shown that the acquired loss of motor control is a consequence of learning-driven dedifferentiation of sensory and motor cortex representations in the forebrain. Humans with acquired hand movement disorders show the same pattern of degraded hand cortical maps as were seen in the primates. This is a predictable consequence for any behavior in which there is a competitive ''winner'' achieved through very stereotypic excitation of skin surfaces, or in which nearly identical, larger sectors of skin are consistently simultaneously activated (Wang et al., 1995; Byl et al., 1996; Nudo et al., 1996; Xerri et al., 1996; Elbert et al., 1998; Merzenich, 2001). Inputs that are nearly simultaneously engaged by a very stereotypic or broadly engaging stimulus will be mutually costrengthened, and their integration will result in larger receptive fields. By natural plasticity processes, the separate, normally differentiated representations of sensory inputs from fingers and palmar surfaces can be largely subsumed by an undifferentiated cortex in which almost any stimulus excites almost any hand-zone neuron (Wang et al., 1995; Byl et al., 1996; Elbert et al., 1998). The behaviors that generate dedifferentiation of cortical hand representations in monkeys are exactly the kinds of hand-use behaviors that generate acquired hand movement disorders in humans (Byl et al., 1996; Byl, 2004).

Positive plasticity-based training reverses acquired hand movement disorders

Using strategies that have much in common with the training conducted on rats described earlier, we developed a behavioral training program to reverse chronic hand dystonias in humans. The training program uses multiple tasks designed to

engage the broad types of sensory inputs that provide feedback for fine hand motor control (Byl et al., 2000). Training begins with sensory discrimination tasks and progresses to graded movements, sensorimotor activities, motor control activities of daily living, fine motor practice, and finally target-specific task practice. Training tasks are progressively difficult and modified by the context, content, force, and mobility of the stimulus while being targeted to a restricted skin surface. All training activities require substantial attention, and success is actively rewarded. With training applied for about one hour per day for 1–2 months, most patients (the majority of whom have been professional musicians) recover relatively normal hand use (Byl and McKenzie, 2000; Byl et al., 2003). Gains with training were independent of the age of the individual. Initial brain-imaging studies indicate that training results in more normal representational topographies and sensory-evoked responses in participants.

These studies strongly indicate that training programs can reverse functional and behavioral losses in fine motor control and sensory input from the hand in adult humans. As in trained rats, such training rerefines grossly dedifferentiated maps of sensory inputs and movement governing sensory-guided motor behaviors.

Up-regulating dopamine cell function in adult rats

Limb disuse exacerbates Parkinsonian symptoms in rat

Parkinson's disease is characterized by progressive motor impairment caused by degeneration of dopaminergic (DA) neurons in the nigrostriatal system (Zigmond and Burke, 2002). Researchers can induce hemi-Parkinsonian symptoms (e.g., slowness or loss of movement on the affected side, preferential use of the nonaffected side) in the rat by unilaterally destroying a percentage of DA neurons in the basal ganglion. These Parkinsonian symptoms are exacerbated by restraining use of the rat's impaired forelimb (Tillerson et al., 2002), suggesting that a decrease in physical activity not only is a symptom of the disease but also contributes to the disease process, perhaps through negative plasticity processes.

Reversing behavioral and neurochemical losses through exercise and exposure to a complex environment

A series of studies has demonstrated that behavioral and environmental conditions can reverse the behavioral and neurochemical losses in Parkinson's-induced rats. One study forced the rat to use one of its forelimbs for a period of time before inducing behavioral and neurochemical deficits in the forced-use limb (Cohen et al., 2003). This forced exercise attenuated the loss of striatal DA neurons and its metabolites in response to inducing degeneration of DA neurons in the rat. A second study forced the rat to exercise its impaired limb after it had been injured, and showed that this exercise reversed the induced behavioral deficits (Tillerson et al., 2003). This recovery from lesion-induced behavioral deficits is paralleled by an attenuation of the depletion of striatal DA neurons in rats (Tillerson et al., 2003). The gains made during the exercise program are lost once the exercise is discontinued, indicating that continuous "therapy" is needed to maintain improvements (Woodlee and Schallert, 2004). Other studies have shown that a motor learning environment (a "rich" environment in which objects in the rat's cage are changed daily) can prevent the progression into Parkinson's-like symptoms in rats whose DA neurons have been destroyed (Bezard et al., 2003; Faherty et al., 2005). This prophylaxis is almost certainly attributable to the heavy, learning-activity-based engagement of surviving DA neurons.

Together, these studies of behavior and neurodegeneration in rat models of Parkinson's disease strongly indicate that the health and vitality of the DA neuromodulatory system is regulated by its own functional activity. A training program of forced use blocks the progression of cell loss and the exacerbation of the down-regulation of DA neuron production and release attributable to motor dysfunction, while symptom progression is reversed. This result opens the door for the investigation of active training programs that go

beyond forced use to revivify DA as well as other neuromodulatory control systems in the brain.

Reversing language learning and reading impairments in children and young adults

Negative plasticity in children with learning and reading impairments

Over the past two decades, brain plasticity studies in monkeys and rats have led to the hypothesis that impaired language development commonly leading to reading problems is often a consequence of an early plasticity outcome by which the cortex organizes its aural speech processing machinery to specialize for the representation of a degraded (noisy) speech model (Merzenich et al., 1993, 1998a, b; Merzenich and Jenkins, 1995). Many inherited neurological faults, as well as consistently degraded inputs from the inner ear, would be expected to result in a muffled or noisy speech model. The ''fuzzy'' phonemic representations behaviorally and physiologically documented in language-impaired children are consistent with this scenario. Moreover, theoretical and animal models of this developmental scenario predict problems in speech representation and language function that are consistent with the behavioral deficit picture presented in most language-impaired and reading-impaired children.

Positive plasticity-based training reverses and young adults with learning and reading impairments

More than a decade ago, researchers posited that these processing deficiencies might be corrected in individuals of any age by appropriate, targeted, and intensive behavioral training. A seven-exercise training program was developed, based on the principles of brain plasticity cited above, to adaptively renormalize speech feature representation and generalize improved processing abilities to all of the syntactic relationships (contexts) that are needed for facile speech reception. About five thousand individuals spanning from about 4 to 18 years of age were given standard assessments testing all aspects of speech reception and language usage before and after training. The results demonstrated large-scale improvements on virtually every language-related cognitive or memory task (Merzenich et al., 1996a, 1998a, b; Tallal et al., 1996a, b). Benefits generalized to aural speech assessments of memory, cognition, and ''processing efficiency,'' and to language usage (Tallal et al., 1996b; Merzenich et al., 1998a). Benefits from training were independent of the age of the individuals (Tallal et al., 1996b; Merzenich et al., 1998a, b).

More than 600,000 children and young adults have now been trained with this program. The conclusion that the training increases representational salience was confirmed by neurological studies that longitudinally reconstructed dynamic cortical responses. fMRI studies revealed that the originally very abnormal response patterns recorded while these children performed key reading and language behaviors could be consistently restored to a more normal form after training. Brain imaging and human recording studies have demonstrated that the neuronal representations of aural speech inputs are substantially more salient, powerful, and reliable after training (Deutsch et al., 2000; Nagarajan et al., 2000; Temple et al., 2001, 2003; Hayes et al., 2003 Nagarajan and Merzenich, unpublished manuscript). Trained children had higher amplitude and more coordinated magnetically recorded responses to the sound parts of words represented within the primary auditory cortex. Event-related potential studies have shown that the discriminable differences that distinguish confusable speech phonemes were renormalized in the average trained child. The level of coherent gamma activity evoked in memory-related tasks, which was grossly abnormal before training, became normal after training in children for both quiet and noisy background conditions.

The four studies described above provide compelling proof-of-principle demonstrations that brain-plasticity-based training programs reverse noisy processing, renormalize temporal and spatial integration constants, enhance functioning of neuromodulatory systems relevant to learning and memory, and improve cognitive performance in a variety of animal and human models of neurological dysfunction. Each of these dysfunctions is

directly relevant to the cognitive challenges faced by older individuals, and each suggests specific aspects of training programs that would be relevant to slow, arrest, or reverse age-related cognitive decline.

Current approaches to treating cognitive decline have limited applicability and efficacy

Two general strategies have been pursued to ameliorate the cognitive changes seen in aging: pharmacological and behavioral. Pharmacological approaches have focused on blocking and possibly reversing the pathological processes that contribute to the physical and functional deterioration of the brain in clinically defined conditions, typically AD (and now, MCI). By targeting one of these hypothesized pathological processes, such as vascular changes, amyloid deposits, or the levels of important neuromodulatory transmitters, it is hoped that adults diagnosed with such diseases can retain memory abilities, cognition, executive functions, and movement control. Behavioral approaches have generally focused on teaching specific strategies in memory and attention to healthy older individuals as well as to those diagnosed with AD or MCI.

Pharmacological approaches

The most frequently applied drugs in patients with MCI and AD are acetylcholine esterase (AChE) inhibitors, which are designed to enhance levels of ACh in the brain by blocking the normal ACh breakdown. Positive benefits provided by AChE inhibitors have been modest. A recent systematic review of clinical trials of AChE inhibitors found that only 10–20% of patients with AD benefited from these drugs, and that high rates of noncompliance among treated patients were commonplace (Kaduszkiewicz et al., 2005). Additionally, the benefit from treatment is only temporary; on an average, patients improve over 3–6 months and return to pretreatment status 9–12 months after treatment initiation (Johannsen, 2004). In patients with MCI, donezepil slows the progression to AD for 12 months, after which progressive functional decline continues at the same rate as control patients (Peterson et al., 2005). Even with the potentially dramatic costs savings that come from delaying AD onset, the cost effectiveness derived from AChE inhibitors is uncertain because of the high cost of these drugs and the fact that all patients still advance, with perhaps a brief delay, to the more advanced stages of AD (Foster and Plosker, 1999).

Research scientists have been working intensely for more than a decade to improve the therapeutic landscape for MCI and AD treatment. There are more than 100 drugs now in the pipeline targeting many different pathological processes believed to contribute to cognitive decline. Other research approaches have investigated strategies for promoting neuron regeneration or replacement using genetic modification or stem cell-based approaches designed to reinvigorate, protect, or grow more new neurons, or to provide new sources of neurons for deteriorating brains. While these approaches are hopeful, no practical strategy is in hand, and Food and Drug Administration (FDA) approval for their use likely will not happen for a number of years.

These investigational paths are promising and will almost certainly lead to improved treatments for AD and perhaps also for MCI. At the same time, none of these future therapies addresses the tremendous problem of normal age-related cognitive decline. In addition, even novel drugs may be only marginally helpful for patients with AD or MCI because they usually address only a single dimension of the complex multidimensional processes of brain deterioration in aging.

Behavioral approaches

A number of studies have suggested that cognitive activity or stimulation could be a protective factor against the functional losses of aging. Because many of these studies were cross sectional, the causal relationship between stimulation and cognitive performance was difficult to establish. In the past few years, however, a number of well-controlled longitudinal studies have shown that participation in cognitively stimulating activities (Wilson et al., 2002, 2003), intellectually complex

work (Schooler et al., 1999), and leisure activities (Scarmeas et al., 2001; Verghese et al., 2003) during adulthood reduces the risk of loss of cognitive abilities in later life. For example, one study measured older individuals' self-reported frequency of participation in a variety of activities, with each assigned an objective level of cognitive stimulation, over a period of 5 years. Older individuals at the highest level of cognitive activity (90th percentile) experienced a 35% less decline in their cognitive abilities than individuals with low levels of cognitive activity (10th percentile) (Wilson et al., 2003). The results of these studies are entirely consonant with the negative brain plasticity viewpoint on age-related cognitive decline, as the cognitive stimulation quantified in these studies would directly affect issues of disuse, noisy processing, weakened neuromodulatory control, and negative learning.

To date, various behavioral training strategies have been proposed to remediate age-related cognitive or memory impairment. The studies evaluating these approaches typically have applied strategy learning to enhance memory function in healthy older adults, with some evidence for success (Yesavage, 1983, 1989; Verhaeghen et al., 1992; Caprio-Prevette and Fry, 1996; Verhaeghen and Marcoen, 1996; Mohs et al., 1998; Glisky and Glisky, 1999; McDougall, 1999). However, these approaches are limited by their approach, and have generally shown small effect sizes, poor maintenance over time, and no generalization beyond the trained skill (Gatz, 2005). More recently, several small trials have been completed that assessed the impact of behavioral training in patients with AD (Davis et al., 2001; Clare et al., 2002; Loewenstein et al., 2004). These studies demonstrated that significant short-term improvements in certain cognitive functions were achievable even in this severely impaired population, although the extent to which these changes generalize more broadly to cognitive and everyday functioning has not yet been established.

It is difficult to fully evaluate the promise of any single behavioral approach as few large, rigorous studies have been conducted to evaluate proposed training programs. A notable exception is the ACTIVE (advanced cognitive training in vital elderly) study, a randomized, controlled trial that evaluated three behavioral training programs (in speed of processing, memory, and reasoning) in older adults (Ball et al., 2002; Edwards et al., 2002). Training in any one of these areas improved performance in that area, but this did not translate to improved everyday functioning possible due to a ceiling effect.

These studies clearly demonstrate the promise of training-based approaches; however, we believe that a more intensive and comprehensive training program explicitly based on the principles of brain plasticity would most likely achieve more robust benefits than have been seen to date. In general, we do not expect that compensatory strategies, or training that targets only higher order cognitive functions, will achieve powerful, sustained effects because such strategies do not address the fact that age-related decline in sensation, memory, cognition, and guided motor control has more fundamental roots in degraded brain processing. Until optimal programs are developed, we believe it is unlikely that a standard of care for a behavioral approach to cognitive decline in aging will emerge.

A novel training program to enhance memory and cognition in the aged

The negative plasticity perspective on the origins of cognitive decline in older individuals immediately suggests a novel approach to treating such cognitive losses. We have built an initial version of a brain-plasticity-based training program explicitly designed to intervene in the downward cycle of negative plasticity by enhancing signal-to-noise ratios and improving neuromodulatory function, while also increasing overall brain stimulation and correcting negative learning. This brain-plasticity-based training program operates on four basic principles.

Strongly engage the brain

To reverse underlying disuse and drive brain plasticity, the program strongly engages the brain with demanding exercises and a daily training schedule. Thousands of trials are required to ensure that the representations of behaviorally important inputs

are coselected or integrated to create robust and complex stimulus-specific and action-event-specific neuronal responses in the cortex. In addition, program exercises employ an adaptive training approach that begins with simplest tasks where there is a high likelihood of success, and proceeds adaptively and incrementally with a series of exercises in which the task demands are made gradually more difficult. Performance within each component is overlearned through repetitive, successful practice with rewards.

Renormalize noisy processing

The training program aims to improve the ability of the brain's auditory and speech systems to engage memory and cognitive systems by enhancing their representational fidelity. Training tasks and stimuli are designed to sharply increase the fidelity and power of representations of complex, dynamic inputs; decrease spatial and temporal integration constants; and directly assure the effective generalization of highly spatially and temporally refined processing to all of the contexts for facile and efficient "complex" (i.e., real) signal reception and memory.

Enhance neuromodulatory function

Program exercises are also designed to strengthen the basic function of each neuromodulatory system component essential for the regulation of learning and memory. Dimensions of behavioral context (arousal, attention, reward, novelty) affect the release of specific neurotransmitters (ACh, dopamine, serotonin, norepinephrine, endogenous opioids) that in turn enable, amplify, and shape plasticity in the adult brain (Merzenich and Jenkins, 1993; Merzenich et al., 1996b; Cahill and McGaugh, 1998; Kilgard and Merzenich, 1998a, b; Bao et al., 2001; Merzenich, 2001; Gibbs and Summers, 2002; Kilgard and Merzenich, 2002; Weinberger, 2003; Schweighofer et al., 2004). For training to be maximally efficient, attentional, reward, and novelty detection system engagement must be closely controlled to achieve near-optimum learning rates. Exercises are specifically designed to engage cholinergic attention systems by requiring temporally focused periods of attended behavior with the goal of stimulating the nucleus basalis in every training exercise cycle (Kilgard and Merzenich, 1998a). Rewards are delivered several thousand times in each daily training session to exercise DA systems in the ventral tegmental area and the substantia nigra (Backman and Farde, 2005). Serotonergic and noradrenergic novelty detection systems are targeted with similar frequency to stimulate the locus coeruleus and the dorsal raphe nucleus.

Strengthen critical life skills

Besides targeting fundamental aspects of brain plasticity, the program aims to guide users out of learned behaviors with negative consequences for brain health and into new behaviors that positively reinforce their enhanced brain function.

Structure of the training program

The overall program is composed of six interrelated training exercises that in aggregate span the acoustic organization of speech. The exercises include the following:

- "High or Low": frequency-modulated sweeps (time-order judgment task)
- "Tell Us Apart": syllables (discrimination task)
- "Match It": short words with confusable stop-consonants (spatial-match task)
- "Sound Replay": short words with confusable stop-consonants (forward-span task)
- "Listen and Do": complete spoken sentences (instruction-following task)
- "Story Teller": complete spoken narratives (narrative-memory task)

Each exercise employs a combination of acoustically emphasized stimuli, adaptive training procedures, and intensive engagement of attentional, reward, and novelty-detection systems. In aggregate, these exercises are designed to improve the accuracy and the speed with which the brain processes speech information, and reengage the neuromodulatory systems that gate learning and

memory. By doing so, we hypothesize that the representational salience of speech input is improved in older brains, that the functional connectivity (feed forward and feedback) between sensory and memory systems would be improved, and that as a result, speech reception accuracy, speed of processing, and memory for speech would improve.

Pilot results from randomized, controlled study

As an initial test of this training program, we conducted a randomized, controlled, pilot study designed to assess the usability of this kind of demanding, intensive program in a classroom environment by older individuals, and to estimate the effect size of intervention on standardized neuropsychological measures of memory.

> We recruited 94 individuals from a local active living community (Rossmoor, CA; aged 63–94, mean age 79.9, mean 16.3 years of education) and, under the authority of an Institutional Review Board, enrolled them into a randomized three-arm study. Participants in the first study (intervention) arm used the program in a classroom setting at its recommended dosing (60 min/day, 5 days/week, 8 weeks). Trainers supervised the classroom to provide technical assistance and general encouragement. Participants in the second study arm (active control) used the same computers and classrooms to watch and listen to educational material presented on DVD. This activity was comparable to program as an active control, in that it engaged participants in an engaging auditory and visual learning activity, was time- and intensity-matched to the intervention, and kept participants blind as to their active control status. The active control attempt explicitly to control neither for the adaptively and progressively challenging nature of program exercises nor for their intense reward and attentional engagement, as we consider those key "active ingredients" in the intervention. Participants in the third study arm (no-contact control) engaged in no-study activities during the training period.
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> All participants completed identical neuropsychological assessment batteries before and after the training period. The primary instrument in this battery was the RBANS (repeatable battery for the assessment of neuropsychological status), a standardized instrument composed of 12 individual subtests covering areas of immediate and delayed memory, attention, visuospatial function, and spoken language. The RBANS has alternate forms designed and tested to be equivalent; we used these alternate forms in the pretraining and posttraining visits to minimize test–retest effects. The assessments in the neuropsychological battery were very different from the training exercises in the remedial program, ensuring that any changes seen in the assessments would represent true generalization of improvement rather than training to the assessment.
>
> Study participants were required to be 60 years of age or older, have a mini-mental state examination (MMSE) of 24 or higher, and have RBANS overall scores to be generally representative of normal aging (taken to be 2 standard deviations within the normative population range, 70–130), and not self-identify with dementia.
>
> Fifty-one participants meeting these criteria were randomized into the experimental group, and 41 completed all training and assessment activities. Four participants withdrew during training citing schedule conflicts; however, no withdrawals cited dissatisfaction with the training programs as a reason for withdrawal (six participants had protocol violations in the posttest condition and were excluded from analysis). All participants were able to learn the usage of the exercises with the built-in training and minor assistance from the classroom trainers; by two weeks into training all participants were using this experimental program without assistance.
>
> Twenty-five participants were randomized into the active control group, and 16 completed all training and assessment activities. There were nine withdrawals over the few days of training citing dissatisfaction with the active control; however, participants completing the active control program were generally satisfied with the material. Eighteen participants were randomized into the no-contact control, and 15 completed all assessment activities with withdrawals due to scheduling

conflicts or moves. The pretraining groups were equivalent in age (one-way ANOVA, $p > 0.4$) and educational level ($p > 0.4$).

Given that the training program focused on renormalizing the auditory system, the primary outcome measure was a global auditory memory score based on the six auditory tests of the RBANS (list learning, story memory, digit span forwards, delayed list recall, delayed list recognition, and delayed story recall). The global auditory memory score was calculated by using the normative RBANS population data to construct age-normed (by decade) look-up tables allowing the conversion of raw score data on each test (which generally showed a strong skew) to scaled score data (optimally normally distributed with a population mean of 10 and a standard deviation of 3). Delayed list recall and delayed list recognition were summed before scaling to allow the inclusion of the significantly skewed and otherwise unscalable delayed list recognition data. The five scaled scores can then be summed to yield a global auditory memory score. These look-up tables were then used to calculate scaled scores and global auditory memory scores for each participant in this study for pre- and posttraining assessments.

Evaluation of the neuropsychological data showed a significant improvement in the global auditory memory score within the trained group (Fig. 2, $p < 0.0005$, two-tailed paired t-test) and nonsignificant trend toward improvement in the active control group ($p > 0.1$) and no significant effect in the no-contact control group ($p > 0.4$). The magnitude of the effect size in this assessment was 0.41, or slightly higher than 1/3 of a standard deviation of enhancement relative to the distribution in the normal population (the standard deviation of the global auditory memory score in the normative RBANS population is 9.0).

The improvement in the global auditory memory score was driven by changes in each of the five scaled score assessments of auditory memory function (Fig. 3). This suggests that the effects of training are broadly distributed across cognitive systems that relay on speech input, as we would predict from the design of the training function.

Another approach for quantifying the effect size is to examine the percentile change in the group relative to the normal population. Using the distribution of global auditory memory scores from the normative RBANS population, prior to training, the trained group scored at the 35th percentile. Following training, the group scored at the 59th percentile.

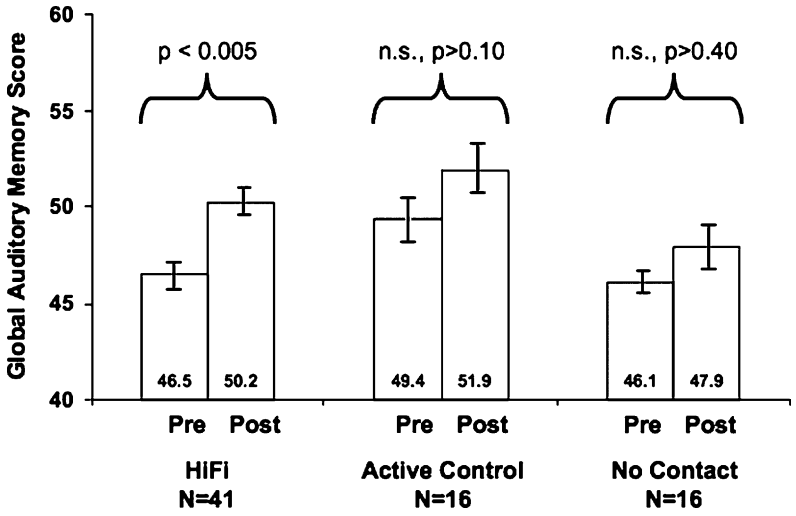

Fig. 2. Brain-plasticity-based training enhances global auditory memory scores in older adults. Pre- and post-training global auditory memory scores for the intervention group (3.7 point change, significant), the active control group (2.4 point change, not significant), and the no-contact control group (1.8 point change, not significant).

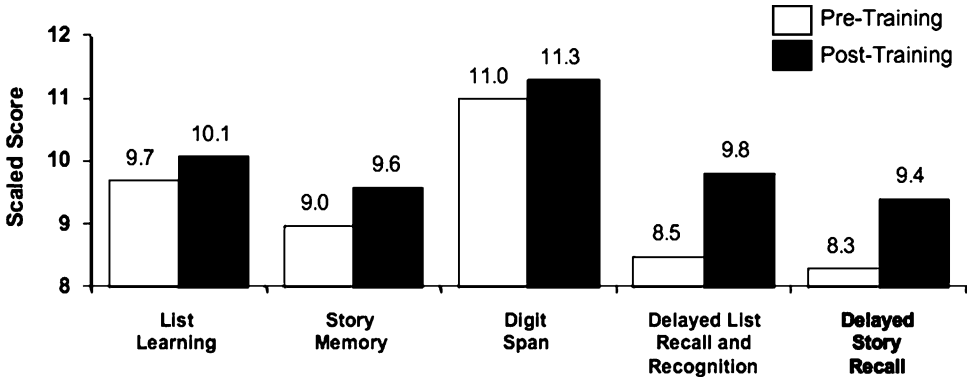

Fig. 3. Memory enhancement is distributed broadly across neuropsychological measures. Pre- and posttraining auditory memory-scaled scores for the intervention group.

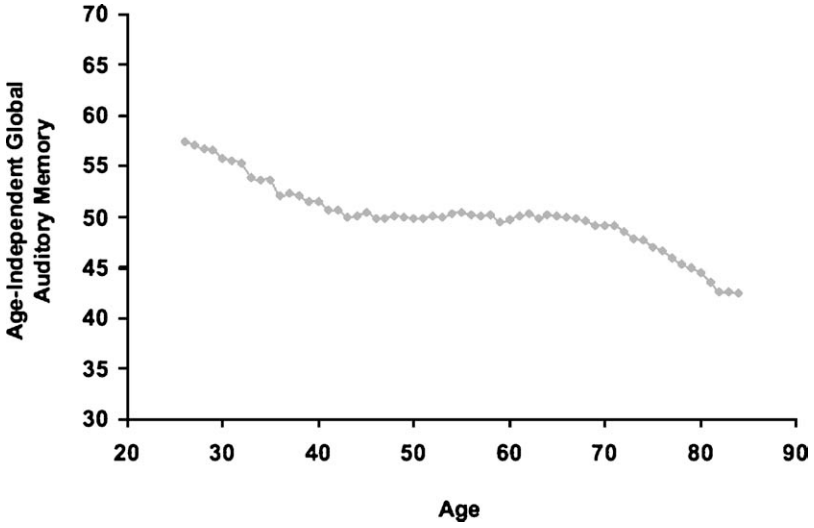

Fig. 4. Age-associated course of decline of memory as assessed with the RBANS. Decline of memory over time was estimated from RBANS normative data by developing scaled score look-up tables for list learning, story memory, digit span, the sum of delayed list recall and delayed list recognition, and delayed story recall based on the entire normative data set including individuals from age 20 to 89. Global auditory memory score was calculated as the sum of the scaled scores. Global auditory memory scores were averaged across a moving window with a width of 10 years to plot the rate of decline of RBANS memory function with age.

To roughly translate this effect size into a measure more relevant for populations undergoing the natural course of normal aging, we might estimate the rate of cognitive decline per year in the normative population and compare the effect size in this study to this rate of decline. We estimated the rate of decline of memory over time from the RBANS normative data by developing scaled scores and a global auditory memory score as described above but based on the entire normative data set including individuals from age 20 to 89 (i.e., not age-stratified by decade as described above). We then averaged this global auditory memory score data set with a moving window with a width of 10 years to plot the rate of decline of RBANS memory function with age (Fig. 4). This function shows an initial decline from 25 to ~40 years of age, followed by a broad plateau, which is followed by a subsequent decline from the age of 62 onwards. The shape of this function suggests

that the RBANS, which was designed for mildly impaired populations, is not likely to be sensitive to the known cognitive changes that occur in middle age and early old age. The slope of the decline in the 62+ period is 0.35 points per year (through age 84, the last year for which the data for full 10 year window is available in the normative data set). The training-induced change in this global auditory memory score is 3.5 points, suggesting that average improvement in the trained group was roughly equivalent to ~10 years of memory performance as assessed with the RBANS. We note that this rough approach is only appropriate at the group level and cannot be used to assess changes at the individual level due to the meaningful test–retest variance for any given individual in the RBANS (and virtually all neuropsychological tests).

In summary, these pilot data demonstrate the promise of this training-based intervention and provide a proof-of-principle to guide larger studies with a wider array of assessments that are fully statistically powered.

Conclusions

The losses in sensory, cognitive, memory, and motor abilities during aging can profoundly affect everyday functioning and quality of life. Because the brain experiences physical deterioration coinciding with the onset of cognitive deficits, it has long been assumed that this atrophy is the sole cause of the loss of cognitive and memory abilities in the aged. The science of brain plasticity suggests a different model of origin of age-related cognitive decline in which the role of physical atrophy is complemented by the interactions of brain disuse, noisy processing, weakened neuromodulatory control, and negative learning.

We have developed an initial version of a brain-plasticity-based training program designed to address the four potential causes of age-related cognitive decline, and in doing so, to enhance auditory perception, memory, and cognition in normally aging individuals. An initial pilot randomized controlled trial demonstrated the feasibility of the approach, in that the intervention was usable, learnable, and well accepted by the target population, and showed substantial promise in the effect size of the memory enhancement.

Going forward, further studies with this training program are required to establish more completely the functional areas and magnitude of enhancement, and in particular to quantitatively assess what broader impact the training has on self-report of everyday functioning measures. Structural and functional brain imaging studies to document the types and magnitudes of brain plasticity underlying the behavioral changes following training will be important as well. Finally, we believe that this training program represents only the first step in the development of a complete suite of training programs that, in aggregate, should target the broad array of sensory, cognitive, memory, and motor problems that emerge with aging.

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