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Plasticity of the aging brain: New directions in cognitive neuroscience

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Cognitive neuroscience has revealed aging of the human brain to be rich in reorganization and change. Neuroimaging results have recast our framework around cognitive aging from one of decline to one emphasizing plasticity. Current methods use neurostimulation approaches to manipulate brain function, providing a direct test of the ways that the brain differently contributes to task performance for younger and older adults. Emerging research into emotional, social, and motivational domains provides some evidence for preservation with age, suggesting potential avenues of plasticity, alongside additional evidence for reorganization. Thus, we begin to see that aging of the brain, amidst interrelated behavioral and biological changes, is as complex and idiosyncratic as the brain itself, qualitatively changing over the life span.

Cognitive neuroscience altered how researchers think about normal cognitive aging. Although some prior research considered preservation or even functional gains in later life, much of the emphasis was on losses accrued with aging: poorer vision and hearing, increased forgetfulness, slower information processing, and more difficulty filtering relevant from irrelevant information. Even though the magnitude of these losses may vary across individuals, differences typically emerge when comparing groups of older adults (here, 60 years and older) to young adults (usually college-aged). With the advent of functional magnetic resonance imaging (fMRI), a noninvasive imaging method that assesses activity in regions of the brain based on measurement of blood flow, cognitive neuroscience research highlighted the plasticity of the aging brain, with changes and reorganization occurring throughout the life span. Although fMRI studies converged with behavioral work to show some losses with age, such as neural regions less active in older adults than in young, it also revealed that older adults could recruit regions of the brain to support cognitive functions in ways unlike young adults (1). Whereas regions such as the left frontal cortex may be specialized in young adults to manipulate large amounts of verbal information in working memory—for example, rehearsing a phone number—older adults exhibited less specialization in their recruitment of neural regions. Although young adults primarily drew on the left frontal cortex for these tasks, older adults also recruited the right frontal cortex, a region typically specialized for visuospatial information, such as remembering a map. Findings of bilateral activation (of both hemispheres of the brain, rather than just one) in older adults, and greater engagement of frontal cortex rather than middle or posterior brain

regions, generated much interest in how the brain adapts to aging.

Cognitive neuroscience reveals plasticity to an extent that was not expected on the basis of behavioral research. Here, the term “plasticity” represents the potential for flexible recruitment of the brain, reflecting structural and functional

changes, sometimes as a response to learning and experiences. One mechanism that could contribute to plasticity is neurogenesis, the growth of new neurons. Reports of neurogenesis occurring throughout adulthood (2) coincided with the emergence of the field of cognitive neuroscience of aging. Although it is uncertain to what extent neurogenesis supports plasticity with age, behaviors such as learning have been shown to increase the survival of new neurons (3). Neurogenesis is not the only mechanism that contributes to the sculpting of the brain with age, and a number of factors have been shown to modify plasticity with age (Fig. 1).

This Review highlights two new directions in the field of aging research with implications for plasticity. The first is the development of new tools to stimulate neural regions. Although cognitive neuroscience methods illustrate how brain activity changes in unexpected ways with aging, manipulation of neural activity is necessary to determine causality. That is, to determine whether patterns of neural activity are critical for cognition, specific brain regions must be able to be stimulated or suppressed. The second section will consider the extent to which these same mechanisms of plasticity extend to social and emotional domains. Although far less studied,

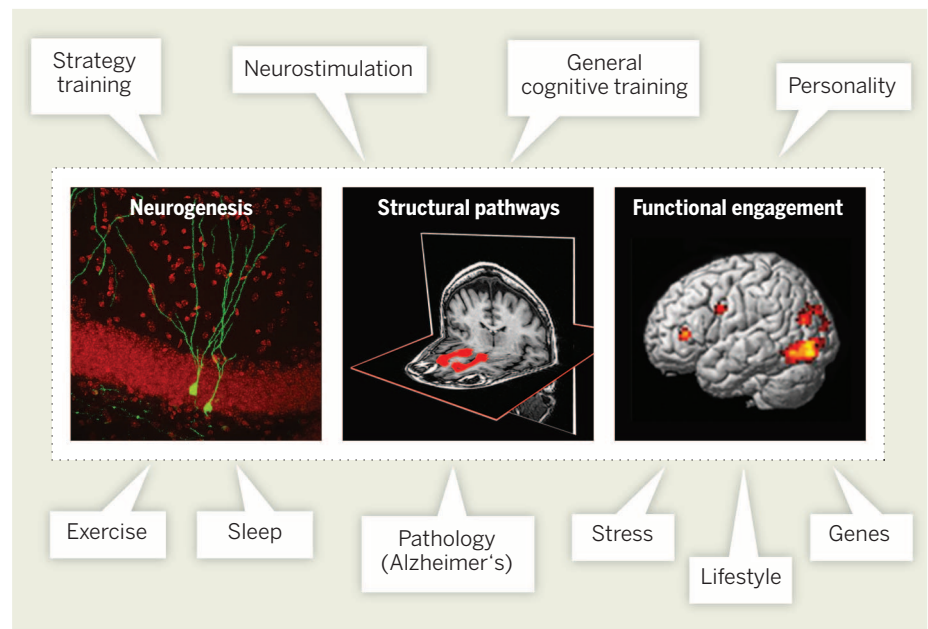


Fig. 1. Mechanisms of neuroplasticity and moderating factors that affect memory with age. The figure depicts three mechanisms (in boxes) through which neuroplasticity could affect memory, and lifestyle factors and interventions (in text balloons) that may modulate some or all of the mechanisms. Neurogenesis—growth of new neurons—may be one mechanism supporting plasticity. (Left) The development of new neurons (in green) in the dentate gyrus in an adult mouse brain. Structural pathways, such as the corticostriatal white matter tracts in the human brain (middle), may be altered through selective pruning or strengthening of connections. Additional structural mechanisms include increases or decreases in volume, as well as the reorganization of existing pathways. Changes in functional engagement include task-based neural activity, such as the regions activated during the encoding of pictures into memory (identified with fMRI of the human brain, right) as well as resting-state neural activity and differential weighting of regions within a network. Although plasticity may be reduced with age (38), a number of factors, such as exercise and stress, have been demonstrated to affect one or more mechanisms of plasticity. [Images adapted from, left to right, (39), (34), and (40), with permission.]

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they are equally important for health and well-being in old age. Together, these two topics reflect the potential for externally administered interventions and internally motivated information processing to capitalize on plasticity in the aging brain.

Manipulation of brain function

Two noninvasive methods of brain stimulation are used to study cognition. Repetitive transcranial magnetic stimulation (rTMS) operates by applying brief electrical pulses to the brain via a coil held over a specific region of a participant's head. Depending on the pulse sequences that are administered, rTMS activates or inhibits neural activity in a region located under the coil (4, 5). Transcranial direct current stimulation (tDCS) (4) uses a battery to administer a small amount of current through two electrodes attached to the scalp (Fig. 2). Both rTMS and tDCS are safe for human participants when operated according to guidelines.

The effects of stimulating the brain can be short-lived or persist for some period of time after stimulation (6, 7). Despite the inability to target small, spatially circumscribed regions or those deep in the brain, these methods hold promise, and applications for healthy and clinical populations are being tested. For example, particular rTMS protocols have been approved in the United States by the U.S. Food and Drug Administration for treating medication-resistant depression. The potential of neurostimulation in cognitive enhancement is particularly promising for cognitive aging. An emerging body of research with healthy young adults establishes that modulating specific brain regions with TMS and tDCS can improve cognitive abilities such as attention, perception, and memory, as shown by faster reaction times and greater accuracy (6, 7). rTMS has the additional potential to improve performance by inhibiting regions that interfere with task performance, such as regions mediating top-down conceptual knowledge that compete with bottom-up perceptual processes (7).

Neurostimulation with age

There are few studies investigating neuromodulation of cognitive abilities in older adults. Stimulating a region can enhance memory performance for older adults, as shown by a study that applied tDCS to the temporoparietal cortex during the learning of objects and their locations on a map (8). The stimulation had no immediate effect on learning. On a follow-up test 1 week later, however, recall of the information was improved when older adults had received tDCS during learning, compared with when they had not. Neuromodulation studies also support the proposition that higher-performing older adults tend to recruit both hemispheres more often than do lower-performers (9, 10), an idea originating from fMRI research.

Results are mixed from the few studies directly comparing the effects of neurostimulation across age groups. Some studies found that older adults can benefit more from neurostimulation than

can younger adults. Name recall for faces was enhanced with tDCS stimulation of the anterior temporal lobes for both younger and older adults, although older adults improved more than did young adults (11). The authors interpreted this as reflecting the possibility that aging weakens cortical connections supporting access to semantic information, such as names, and that tDCS enhanced neuronal firing in a weakened system. Neurostimulation can also disproportionately benefit older adults' learning of motor sequences (12). On this motor task, behavioral training alone may have maximally benefitted young adults, so that tDCS could not further enhance their performance.

Other studies caution that older adults may be more constrained in the benefits from neurostimulation. Whereas young adults' memory performance improves with tDCS stimulation of left or right hemisphere frontal and parietal regions during word retrieval, only left hemisphere stimulation enhanced older adults' (13). Differences in cognitive abilities or life experiences could affect who benefits from neurostimulation with age. For example, older adults with higher levels of education benefitted from tDCS stimulation during a working memory task, whereas those with lower levels of education did not (14). Further investigation of individual differences, such as education or other factors that affect cognitive reserve, may help to resolve inconsistencies across studies.

Neurostimulation can enhance abilities other than memory. Administering tDCS over the dorsolateral prefrontal cortex in the right hemisphere increased older adults' conscious awareness of error commission (15), which is consistent with a role for this region in supporting metacognition, or awareness of task performance, in patients. This approach has translational potential; people may be able to better monitor task performance and correct errors across a variety of different cognitive abilities. To realize this potential, neurostimulation must be studied in conjunction with functional neuroimaging and behavioral research in order to elucidate the cognitive abilities and neural regions that are engaged.

Neuromodulation approaches can be combined with other cognitive neuroscience methods in order to investigate the ways in which neural regions operate together as a network. For example, by targeting a region such as dorsolateral prefrontal cortex with rTMS, one can investigate the impact of disrupting activity in that region on other regions, such as the hippocampus, that constitute the memory network. A study combining TMS and fMRI compared neural engagement when words were encoded with a deep, meaning-based encoding strategy versus a shallow, perceptual encoding strategy (16). Older adults received theta-burst stimulation over the left inferior prefrontal cortex, followed by an fMRI scan. The application of TMS enhanced activity in this region as well as in ventral visual regions—implicated in word recognition—selectively during deep encoding trials. Thus, results establish that TMS not only affects the activity in local regions that are

being stimulated, but also in regions with which they are functionally connected during a task. Another study extended the investigation of connectivity under task-independent conditions. In a study of semantic word generation, older adults exhibited impaired task performance and higher levels of activity in neural regions implicated in the task (17). tDCS ameliorated older adults' neural activity to be in line with that of young adults, and task performance improved to the level of young adults (Fig. 2). To assess the effects of tDCS on the connectivity of the brain, the investigators used resting-state fMRI, which assesses spontaneous fluctuations in brain activity to investigate which regions co-activate during periods of rest rather than during tasks. Whereas anterior regions of the brain exhibited hyperconnectivity for older adults, applying tDCS

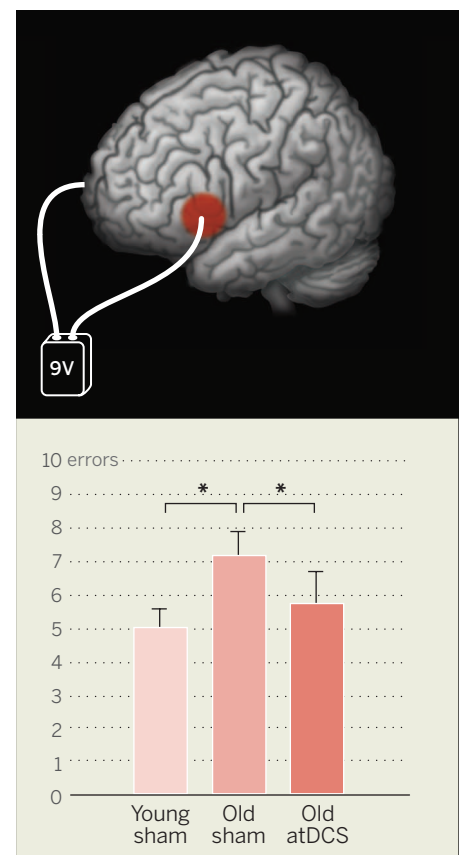


Fig. 2. Administration and effectiveness of tDCS. To administer tDCS, anodal and cathodal electrodes are placed on the scalp (top image depicts the underlying interface with the human brain) and connected to a source of direct current, much like a 9-V battery. When direct current is administered, it can stimulate the underlying region (here, the red circle denotes left ventral inferior frontal gyrus) and improve task performance. (Bottom) With anodal tDCS (atDCS) stimulation, older adults' number of errors on a word generation task is reduced from their performance under sham stimulation and reaches the level of young adults (statistically significant differences denoted by asterisks). [Data published with permission from (17).]

reduced the level of connectivity in these regions, while heightening it in posterior regions. These results suggest that tDCS repaired some age-related changes thought to be disruptive for cognitive tasks.

Limitations and future directions

Despite the potential for neurostimulation studies to advance understanding of which brain regions are causally implicated in cognitive changes with age, few studies investigate aging, and even fewer directly compare younger and older adults. More studies are needed that incorporate multiple age groups, especially from midlife, and converge with findings from other studies to substantiate the effects established thus far. The methods are also limited spatially, in terms of their ability to precisely target localized regions or reach neural regions deep within the brain, such as the hippocampus. TMS cannot be tolerated by participants in all scalp locations, including the forehead, because of twitching and sensitivity.

Neurostimulation holds potential for use as a cognitive enhancer to improve failing memory due to age or disease. For these methods to have real-world impact, critical tests of the time course and longevity of effects are needed. Effects must last longer than experimental sessions in order to be effective at enhancing cognition in everyday life. There are promising results from young adults, with effects persisting over 3 months when tDCS is combined with a five-session motor-skill training regime (18). The time course of the effects may be more limited for older adults as compared with young, posing challenges for extending benefits to cognitively vulnerable populations.

For example, administering tDCS before or during a task was equally effective for young adults, but only administration during the task facilitated reaction times for older adults on a picture-naming task (19).

Ultimately, neurostimulation may prove most effective combined with other methods. Long-term cognitive training may be important to combine with neurostimulation protocols. For example, benefits from face-name training persisted for 6 months in patients with mild to moderate Alzheimer's disease, but these effects primarily reflected the memory strategy training program, with no additional benefit from tDCS (20). It is also possible that training in effective cognitive strategies could be enhanced with other recent neuroimaging approaches, such as neurofeedback. Patients with Parkinson's disease can be trained to increase neural activity in motor regions by using an imagery task with real-time feedback from fMRI (21). If successful memory strategies can be identified through behavioral training and corresponding neural regions can be established by using neurostimulation methods, it may be possible to extend neurofeedback approaches to train more complex memory strategies. It would also be important to directly compare internally guided recruitment of regions through strategies to external stimulation in order to identify the most effective approaches to engage neural regions. Considerations of future directions are provided in Box 1.

Extensions to emotional, social, and motivational domains

Whereas neurostimulation has a fundamentally exogenous influence on plasticity, emotional, so-

cial, and motivational situations may represent endogenous influences. Socioemotional processes may rely on neural systems distinct from cognition for which little is known about the effects of aging, making fMRI and other studies of neural engagement important for understanding age-related changes in these domains. Given some evidence for age-invariant performance, the aging brain may be more plastic for socioemotional than cognitive domains.

For emotion, there is mixed evidence for whether specialized brain regions, such as the amygdala, atrophy more or less than do other regions with age. Evidence is more consistent for age-related changes in functional engagement and connectivity (22). As with cognitive processes, there is a shift to greater engagement of frontal—more than posterior—regions with age (23). Social abilities—including mentalizing about others (what someone

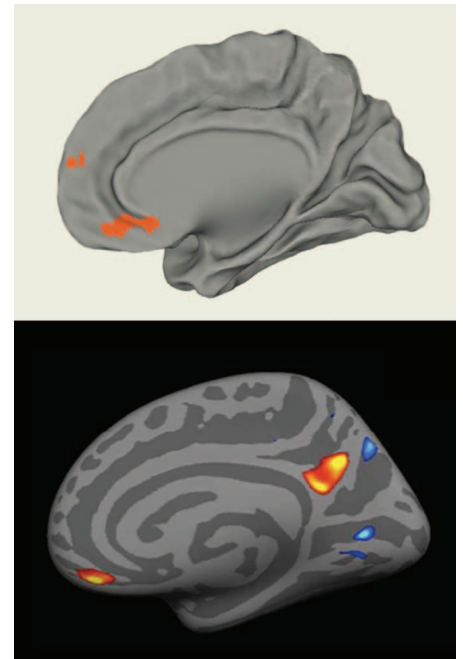


Fig. 3. Age comparisons of social processes.

Whereas some studies find that age differences in neural activity in the human brain extend to social tasks, other studies find reduced age differences for socially relevant information. Moran and colleagues (26) reported age differences in medial prefrontal cortex during moral judgments of stories with negative outcomes compared with a control condition (top; orange areas represent age differences). Cassidy and colleagues (25), however, identified convergence across younger and older adults in a similar region when making socially relevant judgments about other people and their behaviors compared with a nonsocial control condition (bottom; orange areas represent commonalities with age). It is possible that motivational differences contribute to these discrepancies, with negatively valenced information inducing age differences but personally meaningful tasks bolstering neural activity for older adults [as discussed in (29)]. [Images adapted from (26, 25) with permission.]

Box 1. Consideration of future directions.

Questions in neurostimulation and aging

- What is the time period over which effects can persist?
- Is cognitive training necessary to elicit long-term changes?
- Is neurostimulation more effective for some networks or regions than others?
- What precise neural regions are targeted with different sites of stimulation, and how does this affect networks?
- Can performance monitoring, based on training with neurofeedback, be as effective as external stimulation?
- Who benefits the most, and under which conditions? How does this change across the life span?
- How does aging affect which regions should be targeted, in isolation or as part of a network?

Questions in socioemotional cognition and aging

- How distinct are neural regions and processes that mediate socioemotional cognition from other cognitive systems?
- Does aging affect these systems in the same way as other cognitive systems?
- How much do age differences reflect the use of different strategies, rather than changes in the neural systems per se?
- How do social and emotional motivations compare with the predominantly economic motivations studied thus far?
- Which individual difference factors predict better outcomes with age? Do gender, personality, or culture affect outcomes?
- How can neurostimulation be used to probe these systems, which consist predominantly of regions that are not amenable to current methods?

is thinking or feeling), pondering the self, or forming impressions—are only beginning to be investigated with aging. Although some studies indicate that neural regions may be engaged more similarly for younger and older adults on social tasks (24, 25), others find age differences much like other domains (26) (Fig. 3).

It may be most important to understand qualitative differences across age groups in motivation or goals and how these affect neural engagement. Compared with younger adults, older adults prefer positive over negative information, perhaps reflecting a motivation to prioritize feeling good in the time remaining in life (27). Prioritization of positive over negative emotional information with age affects the conditions under which prefrontal cortex is engaged (28, 29). It is also possible that social tasks can be performed more flexibly, making them amenable to different strategies, with corresponding differences in neural regions, across age groups.

Personality could also be important in understanding how age groups differ in their motivations and goals, in that it affects how people construct their environments. For example, neurotic individuals experience stress through high levels of negative emotion (30). Personality also shapes brain development across the life span. Higher levels of conscientiousness are associated with positive outcomes (larger brain volumes, less volumetric decline), whereas higher levels of neuroticism are associated with poorer outcomes (31) when comparing across different age groups. Education, occupation, leisure activities, and high-quality social interactions offer protective effects on behavior with age (30, 32), and presumably also affect the trajectory of brain aging.

The study of motivation and aging largely focuses on economic tasks, involving rewards and losses. Neurotransmitters such as dopamine and serotonin are implicated in economic behavior, and age may reduce the ability to modulate these systems. These neurotransmitters affect the activation of particularly frontal and striatal regions that respond to rewards, risky situations, and delay (thought to discount the value of rewards) (33). Age-related impairments may be greater for losses than gains, which is consistent with the reduced emphasis on negative emotions (27). The integrity of white-matter connections between regions may be particularly important. Better integrity of thalamocortico-striatal pathways is associated with better reward learning and accounts for age differences on the task (34).

Future work can incorporate methods capable of targeting specific neurotransmitter systems [such as positron emission tomography (PET) or pharmacological interventions] to uncover biological causes for other changes in economic behavior with age, such as reduced risk-taking (33, 35). One study using a multimodal imaging approach found that the levels of midbrain dopamine (measured with PET) had opposite effects for younger and older adults on the activation of regions of prefrontal cortex (measured with fMRI). More midbrain dopamine synthesis was related to higher levels of prefrontal activation

for young adults, but less prefrontal activation for older adults (36). This study illustrates the complex relationships between these systems, with baseline age differences in the dopamine system potentially changing the very relationship between dopamine uptake and neural activation.

Conceptualizing motivation more broadly, including consideration of differences in emotional and social goals as well as exploring the response of the motivational system for rewarding social and emotional experiences, will be necessary to understand age-related changes and potential plasticity in these domains (37). These fields have progressed independently, emphasizing different neural regions. Furthermore, there are inherent limitations in studying social processes with cognitive neuroscience methods. Realistic social interaction is limited when movement contaminates data acquisition and participants are tested in a MR scanner. Current neurostimulation methods are not able to reach regions deep within the brain, such as those implicated in many socioemotional processes, although it may be possible to target these regions indirectly through other regions in the network. In studying the effects of neurostimulation, the study of socioemotional processes with age will continue to lag behind the study of cognition. Promising directions are described in Box 1.

Final thoughts

Recent findings of malleable patterns of activation, improved task performance through neurostimulation, and potential preservation in socioemotional domains highlight the plasticity available in the aging brain. Despite this promise, conclusively identifying the conditions that maximally benefit performance will be a challenge when studying such a dynamic and interrelated system. For example, perhaps an effective memory-training program paired with neurostimulation could increase gray-matter thickness and thus affect the functional activation patterns. Improved memory could reduce stress, improving mood and sleep and perhaps even facilitating social interactions and levels of activity. These changes could alter structural pathways and functional engagement of brain regions. In addition, these changes likely operate bidirectionally, dynamically influencing each other in complex ways. We have very little understanding of how these processes affect brain plasticity, let alone the combination of multiple factors and influences that have yet to be identified. Given the qualitative differences in the patterns of neural activity in older compared with younger adults, it is important to investigate these processes across age groups because results from one group are unlikely to translate to others. Last, experiences at different time points throughout the life span could affect later outcomes with aging, making life span and longitudinal studies, in which the same individual is studied over years, crucial to unravel how and when plasticity is available in the aging brain. Just as the advent of cognitive neuroscience increased appreciation of the malleability of the brain in old age, the study of aging can change thinking about the

brain by highlighting the cascading effects of life experiences on plasticity.

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ACKNOWLEDGMENTS

I thank J. Jackson and B. Cassidy for helpful feedback and suggestions.

10.1126/science.1254604