

Aging and neuroplasticity

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Abstract

Neuroplasticity can be defined as a final common pathway of neurobiological processes, including structural, functional or molecular mechanisms, that result in stability or compensation for age- or disease-related changes. The papers in this issue address the aging process, as well as depression, dementia, and stroke and a range of interventions, including manipulations in behavior (physical and cognitive activity/exercise), physiological factors (caloric restriction, cholesterol), pharmacologic treatments (AMPA receptors) and manipulation of brain magnetic fields and electrical activity (transcranial magnetic stimulation, magnetic seizure therapy, and deep brain stimulation). This editorial will address different facets of neuroplasticity, the need for translational research to interpret neuroimaging data thought to reflect neuroplasticity in the human brain, and the next steps for testing interventions in aging and in disease.

Keywords: aging; neuroplasticity; deep brain stimulation; neurogenesis

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Neuroplasticity can be defined as a final common pathway of neurobiological processes, including structural, functional, or molecular mechanisms, that result in stability or compensation for age- or disease-related changes. Translation between studies in animals and in humans and crosstalk between psychiatric and neurologic disease (addictions, mood and anxiety disorders, stroke, traumatic brain injury, and neurodegenerative diseases) is critical to advance interventions to promote neuroplasticity into clinical intervention paradigms. While much of the basic research traditionally focused on “critical periods” of early development, attention has focused more recently on opportunities to induce neuroplasticity in adulthood or during another critical period, the aging process. This editorial will address different facets of neuroplasticity, the need for translational research to interpret neuroimaging data thought to reflect neuroplasticity in the human brain, and in what conditions and when in aging and in a disease process should interventions that induce neuroplasticity be targeted.

Strategies to induce neuroplasticity

The papers in this issue cover aging, as well as depression, dementia, and stroke, and include a range of interventions, including manipulations in behavior (physical and cognitive activity/exercise), physiological factors (caloric restriction, cholesterol¹⁻⁴), pharmacologic treatments (AMPA receptors⁵), manipulation of magnetic fields and electrical activity (transcranial magnetic stimulation [TMS], magnetic seizure therapy [MST], and deep brain stimulation [DBS]^{6,7}). Based on the data presented,⁶ the use of TMS alone or in combination with pharmacologic treatment has great promise in treating cognitive deficits post-stroke and in dementia. Interventions associated with neuroplasticity that merit further preclinical and human study and that would have widespread applicability across neuropsychiatric conditions include epigenetic manipulations (histone deacetylase inhibitors), estrogen, and addressing neuroinflammatory processes.^{7,8-10} While there is a considerable focus on lifestyle and environmental factors associated with enhancing neuroplasticity, there are also modifiable factors that inhibit neuroplasticity and should be a focus of investigation and treatment development, particularly stress.^{1,3}

The important consideration of neurotransmitter interactions and the aging brain is discussed by Mora.³ Preclinical data demonstrate that regional neurotransmitter interactions in functionally connected systems (in this case, glutamate modulation of dopamine and GABA) may change as a function of age, particularly under conditions of stress. There are several important implications of this work. First, in the human brain, the modulation of glutamate in aging and neurodegenerative disease is not well understood, as glutamate has a role in the maintenance of cellular function, as well as cell death.¹¹ Several glutamatergic transporters and receptors play a critical role in synaptic and dendritic plasticity.¹⁰ Secondly, the mechanism of action of psychotropic medications involves actions on the primary target, as well as on functionally linked neurotransmitters.¹² For example, in Parkinson's disease, serotonin neurons in the raphe switch to producing dopamine with levodopa treatment.¹³ Another example are the effects of selective serotonin reuptake inhibitors on post-stroke motor function, for example, which could also represent effects on dopaminergic and glutamatergic systems.¹⁴ Thus, neuroplasticity associated with certain

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interventions (eg, TMS, MST, and DBS) could restore the balance between functionally linked systems or induce a clinical response by having a greater effect on a neurotransmitter downstream from the primary effect.

Measuring neuroplasticity

In preclinical studies, at the molecular level, neuroplasticity is commonly observed as increased expression of synaptic proteins and trophic factors (eg, brain derived neurotrophic factor, BDNF) that lead to neurogenesis and sprouting or remodeling of spine and dendritic architecture.¹⁰ In the living human brain, changes in structural and functional brain imaging are interpreted to reflect neuroplasticity. There are numerous examples in the literature of neuroimaging data interpreted as evidence of neuroplasticity across a range of behavioral or environmental manipulations or interventions, including increased gray matter volumes (volumetric magnetic resonance imaging), increased white matter functional integrity (diffusion tensor imaging), and increased cerebral blood flow or glucose metabolism, particularly increased functional connectivity (positron emission tomography, single photon emission computerized tomography). It is critical that the neuroimaging data be interpreted within the context of behavioral and clinical outcomes to address fundamental issues of functional significance. Specifically, whether increases in brain volume, white matter functional connectivity, or cerebral blood flow/glucose metabolism are associated with clinical meaningful improvements in function. Combined neuroimaging and histopathologic/neuropathologic assessments in animal models and in human brain, respectively, are essential to interpret the neuroimaging data relative to underlying neurobiological mechanisms, particularly to interpret the observed changes as evidence of neuroplasticity.

There are numerous examples in the literature in which novel treatments shown to be effective in patients, based on clinical and/or imaging evidence, have been the focus of pre-clinical investigations for evidence of neuroplasticity or neurogenesis as a mechanism of action. The best example is translational studies on the selective serotonin reuptake inhibitors.¹⁰ More recently, the evidence for a rapid antidepressant action of the N-Methyl-D-aspartate (NMDA) receptor antagonist, ketamine, in treatment-resistant depressed patients had led to preclinical studies that have shown that a single dose of ketamine is associated with increased levels of synaptic proteins and increased

number and function of axo-spinous synapses in rat prefrontal cortex pyramidal neurons.¹⁵ Further neuroimaging studies of the acute antidepressant effects of ketamine would have fundamental implications for understanding neuroplasticity and antidepressant response in the human brain, particularly of the NMDA receptor. There are several examples from the DBS literature of potential effects of DBS on neuroplasticity and associations with clinical benefit. In this issue, Bewernick and Schlaepfer⁷ review the considerable evidence for the antidepressant effects of DBS in treatment-resistant depression and the preclinical data regarding the effects of DBS on hippocampal neurogenesis. Neuroimaging studies performed over the course of DBS have shown adaptive changes in cerebral blood flow in neural circuits associated with depression, which might reflect underlying processes associated with neuroplasticity.¹⁶ Recent work in Alzheimer's disease (AD) has shown that 1 year of continuous DBS (anterior to the columns of the fornix) increased cortical glucose metabolism and functional connectivity, in contrast to the decreased metabolism and decreased functional connectivity observed over the course of AD.¹⁷⁻¹⁸ Preclinical studies of DBS of Papez' circuit demonstrated neurogenesis and release of neurotrophic factors (eg, brain-derived neurotrophic factor; BDNF), which may explain the metabolic effects observed.¹⁹⁻²⁰ Combined studies of TMS and neuroimaging is an important opportunity for translational studies to understand the neurobiology of neuroplasticity and to interpret the human imaging data, particularly given the compelling data presented by Luber and colleagues⁶ on the effects of TMS on cognitive function in normal and compromised states (eg, sleep deprivation). In addition to the need for studies to interpret human neuroimaging data with respect to neuroplasticity, translational studies are also needed to interpret data from other genetic and blood and cerebrospinal fluid (CSF) biomarkers that reflect neuroplasticity (eg, BDNF). The development of biomarkers of neuroplasticity would have important implications for testing whether an individual is an appropriate candidate for an intervention, especially DBS.

Neuroplasticity in aging

While there is evidence for neuroplasticity in the aging animal and human brain, with the exception of memory training programs that are rapidly developing, clinical trials and translation of many of the strategies to promote neuroplasticity are limited. Clinical trials of interventions

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including behavioral and environmental manipulations, pharmacologic strategies (agents with anti-inflammatory, insulin signaling, and glutamate-stabilizing properties, for example) and brain stimulation therapies are an important opportunity to obtain mechanistic information by performing neuroimaging studies and evaluating peripheral biomarkers during the course of treatment in both preclinical models and humans. Maximizing the effects of such interventions is obtained from the study of neurodegenerative diseases and may be applicable to aging. With respect to the timing of the intervention, several lines of evidence indicate that the effects of an intervention can be maximal soon after brain injury or in the early stages of a disease process. In the case of stroke, the greatest benefit from rehabilitation is observed soon after injury, at which time in animals rehabilitation efforts can capitalize on the short time window of neuroplasticity that has been demonstrated to occur.²¹ Similarly, in the areas of AD and cognitive aging, studies are now focused on prevention in “asymptomatic” individuals at risk based on family history or genetic or neuroimaging evidence of a neurodegenerative process. Early intervention in such individuals may protect against the loss of synapses and dendritic spines that occurs secondary to β -amyloid deposition.²² Depressive or other neuropsychiatric symptoms (eg, anxiety, irritability) may also represent a focus for

early intervention. Major depression has been described as a disorder of neuroplasticity.⁷ Importantly, depression is a prodromal sign in many neurodegenerative diseases and might signal impaired plasticity and vulnerability to the development of motor and cognitive symptoms.

Conclusion

In summary, a continuum of interventions has been investigated that demonstrate neuroplasticity in preclinical models. Translational studies in preclinical and human models that combine neuroimaging with histological or neuropathological analyses are needed to confirm that structural and functional neuroimaging data in humans actually reflect neurogenesis. In addition to these comparative studies, multi-modality neuroimaging studies to compare structural and functional change to molecular and neurochemical processes will advance our understanding of the nature of neuroplasticity in humans. Having validated these interventions, including the effects of behavioral and environmental manipulations and brain stimulation, there will be unique opportunities to use the neuroimaging methods to develop treatment algorithms based on a combination of interventions, as well as to identify “at-risk” individuals for prevention trials. □

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