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Brain Plasticity and Genetic Factors

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Abstract

Brain plasticity refers to changes in brain function and structure that arise in a number of contexts. One area in which brain plasticity is of considerable interest is recovery from stroke, both spontaneous and treatment-induced. A number of factors influence these poststroke brain events. The current review considers the impact of genetic factors. Polymorphisms in the human genes coding for brain-derived neurotrophic factor (BDNF) and apolipoprotein E (ApoE) have been studied in the context of plasticity and/or stroke recovery and are discussed here in detail. Several other genetic polymorphisms are indirectly involved in stroke recovery through their modulating influences on processes such as depression and pharmacotherapy effects. Finally, new genetic polymorphisms that have not been studied in the context of stroke are proposed as new directions for study. A better understanding of genetic influences on recovery and response to therapy might allow improved treatment after stroke.

Keywords

ApoE; BDNF; genetics; plasticity; rehabilitation; stroke

Stroke is the leading cause of serious, long-term disability in the United States, affecting 5.8 million stroke survivors in the United States alone. More than 75% of those who survive stroke suffer disability severe enough to affect employment, and 80% suffer motor impairments requiring rehabilitation. Although motor rehabilitation therapy is recommended for most stroke survivors, results of this therapy are highly variable between individuals. Understanding factors related to motor recovery and increasing the efficacy of motor rehabilitation strategies could drastically improve quality of life for many stroke survivors.

Successful motor recovery requires plasticity in many areas of the brain. Brain plasticity includes the capability of neural circuits to alter their functional organization in response to experience and is a crucial component of both functional recovery after injury and skill learning in healthy individuals. Reorganization and remapping of both affected and unaffected brain areas serve recovery, observed most readily in the chronic phase of stroke. Throughout the early phases of stroke and rehabilitation, neural networks are gradually

restored to some degree around the lesion itself, while secondary brain regions in a distributed network are often recruited to progressively compensate and, depending on the extent of damage to a given region, may perhaps adopt some of the functions of the damaged area. When injury is restricted to white matter, many of the same changes are apparent in the overlying gray matter.– Such cortical plasticity occurs in many different forms, from synaptic plasticity at the cellular level to map plasticity at the organizational level. Functional reorganization emerges from neuronal processes, such as synaptic plasticity, which in turn are driven by specific intracellular and extracellular neural signaling pathways. Plasticity is crucial to recovery and learning, but the rates and extent of recovery and learning vary considerably between individuals. Whereas individual factors such as lesion size and location, mechanism of infarct, functional magnetic resonance imaging (fMRI) activation patterns, and demographics like age all affect the extent and rate of recovery,, the underlying neural mechanisms remain incompletely understood.

With such a multitude of molecular events being related to recovery, not surprisingly a number of genes have been suggested as important to variability in stroke recovery. Genetic variation in any of these components could thus influence each individual's capacity for brain plasticity and could explain the variability encountered in motor rehabilitation efficacy. Those individuals with a greater capacity for adapting and favorably altering cortical connections have a theoretical advantage with regard to stroke recovery. Further, genetic differences may also influence the amount or type of rehabilitation therapy required to induce cortical plasticity and concomitant functional recovery. This emphasizes the need for a precise understanding of the factors that can favorably influence plasticity and the relationship between these factors and the capacity for functional recovery.

Forms of Brain Plasticity and Their Measurement

Brain plasticity in the central nervous system (CNS) can be described at several different levels. At the cellular level, plasticity can be observed as changes in the number and/or strength of synapses that can in turn be manifested at a neural network level as reorganization of representational maps.

A number of events underlie plasticity at the cellular level. At the synaptic level, plasticity can occur in relation to increased dendritic spine formation, pruning, and remodeling; calcium channel regulation; changes in NMDA receptors; or changes in AMPA receptor trafficking. A commonly studied example of plasticity at the cellular level is long-term potentiation (LTP), that is, the long-lasting enhancement of synaptic strength between two neurons that can result from application of high-frequency stimulation to a presynaptic excitatory pathway.

These cellular events can be influenced by experience and environment, for example, complexity of the housing environment,, maze training, avoidance conditioning, and sensitization. Increased protein and RNA synthesis– support these events. Study of such molecular/cellular plasticity events in humans is very difficult, but this issue can be approached by considering the genetics of such syntheses by physiological and human brain

mapping approaches. In these cases, synaptic plasticity within individual neurons is often inferred from measures taken across large populations of neurons.

Plasticity across neural networks in humans can be studied with a number of methods. Common examples include transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). These techniques have been used to probe cortical excitability, short interval cortical inhibition (SICI), intracortical facilitation (ICF), paired associative stimulation (PAS), representational map size, and movement directional targets.– One example of such physiological plasticity involves serial measurement of SICI or ICF. A motor map can be evaluated by using TMS to measure the motor-evoked potential (MEP) in 1-cm increments along a grid placed over the scalp, then reassessed following an intervention in order to measure short-term plasticity. Another motor-TMS paradigm involves stimulating a site in the cortex that controls thumb movement, measuring the direction of movement, and then “training” the thumb in the opposite direction. Following training, TMS stimulation of this same site results in more evoked thumb movements in the direction of training.

Plasticity of cortical representational maps has been studied in animals, across a wide range of motor and sensory domains., A key method for its measurement has been intracortical microstimulation.– Nudo et al mapped the area of primate M1 that evoked a response in either the muscles of the digits or those of the forearm; monkeys then underwent training for either a skilled digit task (pellet retrieval) or a forearm task (key turning), and M1 was remapped. The authors found that training in each specific behavioral task differentially altered movement representations, with digit task training specifically associated with expansion of finger movement representations and forearm task training specifically associated with expansion of forearm movement representations. These map changes were accompanied by an enhancement in performance on the trained task. Similarly in rats, Kleim et al found that rats performing a skilled reaching task showed expanded distal forelimb representations and more synapses per neuron compared to rats performing an unskilled reaching task. Enhancements in task performance accompanied map expansion and synaptogenesis. Animal studies also suggest that motor map plasticity is characteristic of, and may be crucial to, rehabilitation success after stroke.

In humans, a number of methods have been used to study cortical map plasticity after stroke, including fMRI, positron emission tomography (PET), and TMS. Overall, these studies suggest that after stroke, reorganization of function can occur in surviving tissue that surrounds an infarct and in distant areas such as nodes in a distributed network and homologous regions in the contralesional hemisphere. Measurement and interpretation of poststroke plasticity in humans have been reviewed elsewhere.,–

The interrelationship of these measures of plasticity suggests that individuals with a greater capacity for synaptic plasticity, dendritic branching, protein and RNA synthesis, synapse formation, physiological changes, and map reorganization may be more likely to experience greater behavioral improvements following stroke. Because many of the neural signals driving plasticity involve the activation of specific genes, genetic variation in humans might

influence the expression of these plasticity-related events and thus their impact on reducing disability in humans after stroke.

Genetic Factors Affecting Plasticity

Either directly or indirectly, genetic factors might have an influence on many of the processes related to brain plasticity. These likely have a variable relationship with nongenetic factors that have been shown to influence brain plasticity, such as age, experience, mood, features of CNS injury, severity of behavioral deficit, training intensity, medication effects, social factors, and even the point in the estrous or menstrual cycle.,–

The human genome has a number of polymorphisms, or common and different versions, for genes that influence plasticity through diverse mechanisms. This genetic variation might allow for identification of markers that may predict an individual's capacity for brain plasticity and thus potential for recovery following CNS injury such as stroke. Knowledge of such markers might allow investigators to (a) study the biological role of a particular protein via polymorphisms that enhance or decrease its efficacy, (b) design novel treatments based on experimentally manipulating the activity of a protein in a similar way a gene variant does endogenously, (c) predict which patients would be most likely to benefit from such interventions based on the presence or absence of these polymorphisms, and (d) identify biologically distinct subpopulations prospectively, which might be of particular value to clinical trials. Two specific candidate genes toward these goals are considered below: a single nucleotide polymorphism (SNP) on the gene for human brain-derived neurotrophic factor (BDNF) and the group of SNPs on the gene for apolipoprotein-E (ApoE) resulting in the gene variants $\epsilon 2-4$. Following this, several less studied but potentially important genetic polymorphisms will be explored.

BDNF

BDNF is the most abundant growth factor in the brain. It is involved in plasticity directly through its modulation of cellular processes as well as indirectly through its modulation of other processes that influence plasticity such as depression. Its direct involvement will be discussed here and indirect involvement will be covered in a subsequent section.

The direct involvement of BDNF in brain plasticity is related to both short- and long-term influences.– Shortly after being released, BDNF can rapidly depolarize postsynaptic neurons and elicit short-term postsynaptic effects on ion channels and NMDA receptors, in addition to potentiating excitatory synaptic transmission by promoting presynaptic neurotransmitter release.– In the long-term, BDNF can induce lasting changes in synaptic plasticity, neurotransmitter and neuropeptide production, and excitability.– BDNF is crucial in development but plays an important role in adulthood as well by modulating neuronal structure, function, and survival; enhancing synaptic transmission; facilitating long-term potentiation; and mediating use-dependent plasticity.–

Decreased BDNF levels in the brain have been associated with numerous functional deficits, providing further insight into the role of BDNF. BDNF heterozygote mice fail to form new synapses or modify the balance between excitatory and inhibitory synapses in the

somatosensory cortex following 24 hours of whisker stimulation, whereas control mice undergo these structural changes. Inhibition of BDNF via gene knockout or infusion of antisense BDNF impairs spatial learning and memory in rodents,– and blocking BDNF in the hippocampus erases the cognitive benefits of exercise. Injecting antisense oligonucleotides, receptor antagonists, or BDNF receptor antibodies into the motor cortex to inhibit BDNF function results in impaired skilled motor performance and disrupted cortical reorganization., Subsequent application of exogenous BDNF in the motor cortex can partially restore motor skill acquisition and motor cortical movement representation. Together, these observations emphasize the role of BDNF in modulating the functional organization of the cortex.

BDNF levels can increase in relation to a number of experience and environmental stimuli. In rats, spatial learning and contextual fear conditioning both increase BDNF mRNA and protein in the hippocampus.,– whereas amygdala-dependent fear conditioning increases BDNF mRNA in the amygdala and whisker stimulation results in enhanced BDNF mRNA expression in barrel fields corresponding to the stimulated whisker. Rodent studies have shown increased BDNF in motor cortex following motor learning. Similarly, monkeys undergoing motor learning show motor map reorganization associated with region-specific upregulation of BDNF expression, suggesting that BDNF is capable of altering cortical connections at a very specific level in response to experience., These studies emphasize the specificity of stimuli and of spatial effects in the CNS.

BDNF is important to many forms of plasticity in relation to repair of neurological conditions.– BDNF and its receptor TrkB have previously been used as markers of motoneuron survival and neuronal plasticity.– In a mouse model of spinal cord injury, BDNF expression provided a neuroprotective role, and BDNF levels have been associated with CNS repair in several rodent stroke models.– Treatment with exogenous BDNF is associated with better motor recovery. These findings suggest that influences on CNS levels can influence plasticity and thereby affect recovery of function after stroke.

A functional SNP (rs6265) has been identified in the BDNF gene, in which a G to A substitution at nucleotide 196 results in an amino acid switch from valine to methionine at codon 66 (val⁶⁶met). Approximately 30%–50% of the population is either heterozygous (Val/Met) or homozygous (Met/Met) for this BDNF val⁶⁶met polymorphism. The SNP occurs in the 5' prodomain of the BDNF gene, a region that encodes the precursor peptide proBDNF, which is later cleaved to form the mature protein. Assuch, the polymorphism affects neither mature BDNF protein function nor constitutive release but rather the intracellular trafficking of pro-BDNF is dramatically altered, affecting experience-dependent BDNF release.,

The val⁶⁶met polymorphism has been associated with abnormal cortical morphology. Structural MRI studies of healthy humans have linked the Met allele of this polymorphism with reduced volume of temporal and occipital gray matter, prefrontal cortex, and hippocampus.– In Asian subjects, the Met allele has been associated with decreased volumes of the parahippocampal gyrus and the caudate nucleus. These differences may be related to the role of BDNF in development, to effects of continued plasticity throughout the lifespan,

or both., Volumetric differences could arise through any combination of changes, including decreased dendritic complexity, fewer neuronal and supporting cells, and increased cell death or decreased neurogenesis during development or over the lifespan. BDNF and its receptors have been shown to be important in mediating all of these processes.

In addition to modifying cortical structure and function, the BDNF val⁶⁶met polymorphism has been associated with behavioral effects, primarily in the domain of hippocampal-dependent memory. Using a battery of neuropsychological tests, Met allele carriers (those with one copy of the polymorphism, i.e., Val/Met; and those with two copies, i.e., Met/Met) as compared to noncarriers (i.e., Val/Val) have been shown to have poorer performance on episodic memory tasks that involved recalling places and events but no differences on tasks that have been classically shown to be less hippocampal-dependent, such as word learning, semantic memory, verbal fluency, and working memory/executive function planning tasks.,,,

A good deal of research conducted thus far has examined effects of the BDNF val⁶⁶met polymorphism on the hippocampus, but BDNF and its TrkB receptor are widely distributed throughout the brain and the BDNF val⁶⁶met polymorphism has been shown to broadly influence physiological and experience-dependent forms of plasticity.,

A study by Kleim and colleagues investigated how the BDNF val⁶⁶met polymorphism influences plasticity in the motor cortex. This study used TMS to study the motor cortex representational map for a hand muscle before and after short-term motor practice. Whereas subjects in the different BDNF genotype groups showed similar organization of motor maps at baseline, Met allele carriers showed reduced short-term, experience-dependent plasticity by several measures. Similarly, McHughen et al examined the effect of the BDNF val⁶⁶met polymorphism on the same short-term experience-dependent plasticity paradigm, but used fMRI, and found similar results in many brain regions. Given the importance of cortical reorganization in the motor system following stroke, these findings suggest that this polymorphism might affect poststroke recovery potential, though studies of polymorphism effects in long-term models of plasticity are needed.

Further evidence, across several plasticity-inducing paradigms, comes from a study by Cheeran and colleagues. These authors used several brain stimulation paradigms to study the effect of the val⁶⁶met polymorphism on physiological plasticity. The authors utilized the repetitive TMS (rTMS) techniques: continuous theta burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS). Bursts of three stimuli at 50 Hz are given continuously at a rate of five bursts per second during cTBS, which suppresses corticospinal excitability. Such bursts given in 2-second trains constitute iTBS, which is excitatory. Using either cTBS or iTBS, they found that cTBS suppressed MEPs and iTBS facilitated MEPs as expected in Val/Val subjects; however, no difference was found in non-Val/Val (Val/Met or Met/Met) subjects with either paradigm. Carriers of this val⁶⁶met polymorphism also did not show homeostatic plasticity after tDCS or facilitation with paired associative stimulation.

These polymorphism-related findings raise speculations as to potential clinical implications. Evidence supports a role for BDNF in CNS repair after neurological injury such as stroke, traumatic brain injury, spinal cord injury, and Alzheimer's disease. The Met allele has been

associated with a poorer outcome following subarachnoid hemorrhage; among individuals with no cerebral infarction, Met carriers performed worse on tests of learning and memory., This raises the concern that if the 30% of humans carrying at least one Met allele have abnormal BDNF release and responsiveness, these individuals might have decreased CNS repair and thus poorer functional recovery following neurological insult.

It is clear from studies in both animals and humans that BDNF and the BDNF val⁶⁶met polymorphism play a role in brain plasticity. Future studies might examine how these findings relate to functional recovery after stroke and the therapeutic implications.

ApoE

ApoE is primarily involved in lipid transport from one cell type or tissue to another, though it also plays a significant role in the growth and regeneration of peripheral and CNS tissues and in modulating neuronal repair, remodeling, and protection., There exists a set of two common SNPs on the human ApoE gene, one at amino acid position 112 and one at position 158, which result in three distinct alleles, termed ϵ 2–4 or ApoE2–4. The most common allele, ϵ 3, has a cystine residue at position 112 and an arginine at position 158; ϵ 2 has a cystine at both positions and ϵ 4 has an arginine at both positions. The most common genotype, E3/E3, ranges in frequency between 43% and 74% of humans depending on ethnicity. Approximate frequencies for less common genotypes are as follows: 22% E3/E4, 12% E2/E3, 3% E4/E4, 2% E2/E4, and 1% E2/E2.,

Studies in animal models and cell culture suggest that ApoE is important in CNS plasticity. ApoE levels are elevated following olfactory bulb lesion, and ApoE knockout mice show delayed and diminished synaptic recovery following olfactory bulb lesions compared to wild type mice. A study examining synaptic plasticity using entorhinal cortex lesions found that transgenic mice expressing human ApoE4 had substantially less compensatory sprouting and reactive synaptogenesis than those mice expressing human ApoE3. In human neuronal cell cultures, adding nerve growth factor (NGF) plus ApoE3 enhanced neurite outgrowth, while NGF plus ApoE4 did not. A study of postmortem human brains from patients with Alzheimer's disease found that patients with the ApoE4 allele showed higher levels of neuronal loss than those lacking ApoE4 and impairment of neuronal remodeling. This study also found a gene-dose effect, with the highest levels of neuronal loss occurring in E4/E4 individuals.

In humans, the ApoE4 allele is highly implicated in the risk for Alzheimer's disease, with individuals carrying one or more ApoE4 alleles being much more likely to have Alzheimer's disease and have an earlier age of onset as well., One theory of the involvement of ApoE in Alzheimer's disease is that ApoE3 facilitates the clearing of A β plaques and tangles at a much higher rate than ApoE4. Expanding beyond this, other studies have shown that the ApoE4 allele is linked to accelerated cognitive decline with age, impaired episodic memory, decreased hippocampal volume and cortical thickness,– and memory, cognitive, and attentional impairments on other measures, (for review, see Parasuraman). Additionally, individuals carrying the ApoE4 allele have shown fMRI and PET activation patterns similar to patients diagnosed with Alzheimer's disease.,

These data related to ApoE genotype effect on brain morphology and cognitive function suggest that this polymorphism might affect brain plasticity after stroke as well. Studies examining the relationship between ApoE genotype and outcome after severe traumatic brain injury (TBI) support this. In a prospective cohort study, Teasdale and colleagues found that patients with the ApoE4 allele were more than twice as likely to have an unfavorable outcome 6 months after TBI as were those without this allele. A recent meta-analysis concluded that the presence of the ApoE4 allele was associated with increased risk for poor long-term outcome following TBI. Another meta-analysis examined outcome after subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), or ischemic stroke and found no overall influence of ApoE genotype on death or dependency in the 3 months post stroke. This analysis did find an effect of ApoE genotype on outcome following SAH specifically but not ischemic stroke. However, in a recent study of 241 patients with stroke followed as part of a clinical trial, ApoE genotype was associated with outcome at both 1 and 3 months following stroke but not at baseline, with ApoE4 associated with worse outcome.

Even though the relationship between the ApoE polymorphism and poststroke plasticity has not been directly studied in humans, animal studies and acute stroke recovery studies point to its importance in plasticity and recovery. Further studies are needed to clarify the significance of ApoE genotype on plasticity and outcome after stroke in humans.

Genetic Factors Are Involved in Many Processes Influencing Plasticity

Factors such as learning, attention to task, depression, and type of intervention are integrally related to the process of brain plasticity, and each has its own set of relationships with genetic factors.

Learning

Recovery of function after stroke relies on mechanisms similar to, and in some cases directly overlapping with, those underlying normal learning. Furthermore, learning is often a key component of poststroke therapy. As discussed throughout this review, the BDNF val⁶⁶met and ApoE ε2-4 polymorphisms have been shown to modulate cognitive and motor learning in healthy subjects, and some catecholamine gene polymorphisms affect cognitive and likely motor learning as well.

Attention to task

One key moderator of plasticity is task salience and attention to task. This is seen in animals, where reward gated attentional valence and influenced plasticity, and in humans with the paired associative stimulation TMS paradigm, which elicits plasticity only when the subject is paying attention to the paired stimulus. Because rehabilitation generally involves intense and repetitive activity over a long period of time, constant attention can be difficult. Polymorphisms in genes related to dopamine, steroid sulfatase, acetylcholine, and ApoE have all been linked to attention. In support of this, several studies of children with attention deficit hyperactivity disorder (ADHD) have generated considerable evidence that the dopaminergic system and polymorphisms affecting it are involved in attention modulation,

particularly because inattention is a hallmark symptom of ADHD, and tests of attention can be used as endophenotypes.–

Another gene recently associated with inattention is the X-linked steroid sulfatase (STS) gene. Deletion of this gene results in a higher likelihood of ADHD, particularly the inattentive (non-hyperactivity) subtype. Recently two polymorphisms on the gene have been associated with ADHD in children having the combined or inattentive subtype.

A cholinergic receptor gene, CHRNA4, and the ApoE ϵ 2–4 polymorphisms have also been implicated in spatial attention, speed of attentional reorienting, and sustained attention, and ApoE genotype has been shown to modulate attention in healthy middle-aged individuals.

To combat inattention, robot studies often combine therapeutic maneuvers with highly salient virtual reality games. This type of salient therapy may involve the dopaminergic system and therefore may be modulated by dopamine-related polymorphisms.

Several polymorphisms are related to abnormalities in attentional control, as evidenced by their association with ADHD. Some of these genes may affect a patient's ability to pay attention to rehabilitation training and therefore affect plasticity and the efficacy of such training. In subjects with stroke, it is likely that attention to rehabilitation is to some extent modulated by the effects of depression and related emotions.

Depression

Depression is a serious condition affecting 12% of men and 20% of women, but anywhere from 20% to 79% of stroke victims, depending on the measure used to assess the patient., Stroke patients with concurrent depression show worse functional recovery and are 3.4 times less likely to survive the first 10 years after stroke., Several factors influence poststroke depression, including age of onset, gender, lesion location, social support, psychiatric history, stroke severity, and functional outcome, but genetics are likely influential here as well. Depression is a multifaceted illness, and several genetic factors have emerged as potential risk factors, particularly in the context of gene-environment interactions.,

One logical step is to examine the effects of polymorphisms in the monoamine neurotransmitter systems, particularly serotonin. Depression has been suggested by some to be often related to a deficiency in serotonin or norepinephrine, because presently the most effective antidepressant drugs act by increasing their levels in the CNS. One key polymorphism, termed 5-HTTLPR, is found in the serotonin transporter gene SLC6A4 and occurs in either a “long” or “short” form., The short form, which arises from a 44-bp deletion, results in less serotonin transporter synthesized and therefore reduced uptake in the presynaptic neurons. Studies have linked the 5-HTTLPR short allele with depression and vulnerability to stress. This and several other serotonin-related polymorphisms are examined in several reviews., Caution should be used in interpreting genotype results, as there are many negative studies also. In the 1953-patient STAR*D (sequenced treatment alternatives to relieve depression) study, 768 SNPs were examined for their relationship to major depression, and only one SNP in the gene for serotonin receptor 2A was significantly

associated with treatment response, although such high-throughput analyses have their drawbacks as well.

The BDNF val⁶⁶met polymorphism has also been studied in relation to depression; although studies show mixed results, they generally point toward higher susceptibility to depression with the Met allele. Geriatric depressed Taiwanese and American subjects have been shown to have a higher incidence of the Met allele, but this association was not replicated in either Chinese, or German populations. Frodl et al suggested that the lower hippocampal volumes associated with Met allele carriers might make these subjects more susceptible to depression, consistent with the observed reduction in postmortem BDNF levels within hippocampus and prefrontal cortex (PFC) of depressed patients. Additionally, among subjects with treatment-resistant depression, repetitive TMS has been shown to improve depression symptoms in Val/Val subjects to a significantly greater extent than Val/Met or Met/Met subjects, a suggestion that treatment strategies may differ between the two groups.

Type of therapy

Exercise therapy—Therapy including exercise would take advantage of the positive relationship between exercise, BDNF, and brain plasticity. Exercise increases BDNF mRNA and protein in cerebral cortex, cerebellum, and spinal cords of rodents, sometimes in as little as 30 minutes. In humans with spinal cord injury, multiple brain regions show activity-dependent increases in BDNF levels following 10 to 30 minutes of activity. Seeing that exercise has been shown to upregulate BDNF, including exercise therapy in a stroke patient's daily routine may have a positive impact on plasticity. Initial evidence suggests that the BDNF val⁶⁶met polymorphism modulates response to exercise. Such an interaction suggests that various therapy strategies may differentially impact patients of each genotype, and therefore genotype could be used to guide therapy choice.

Pharmacotherapy—A number of different drugs have been examined as pharmacological means to improve function after stroke, particularly agents that affect monoamine neurotransmitters; genetic factors can be strong determinants of drug effects. Drugs studied include the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram, the norepinephrine reuptake inhibitors maprotiline and reboxetine, and catecholamine enhancers such as amphetamine, levodopa, and methylphenidate. An understanding of the interaction between relevant polymorphisms and pharmacotherapy effects will allow treatment options to be tailored to the individual patient. As an example, Mattay and coauthors found a differential effect of amphetamine administration on cognitive performance between subjects with and without a val^{108/158}met polymorphism in the gene for the enzyme catechol-O-methyl transferase (COMT), which affects the level of catecholamines in the CNS (described in detail below). Amphetamine improved performance in subjects carrying both Val alleles but degraded performance in subjects carrying at least one Met allele. Another drug used in the context of stroke recovery is methylphenidate, and a polymorphism in the dopamine transporter protein has been shown to affect TMS response to methylphenidate in children with ADHD.

In a similar manner, several serotonin-related genes have been studied for their effects on response to fluoxetine and citalopram. Peters and colleagues found that polymorphisms and SNP haplotypes in genes for the enzyme tryptophan hydroxylase, the serotonin transporter protein, and serotonin receptor genes all predicted response to fluoxetine, though these same polymorphisms had no effect on citalopram response in the large STAR*D clinical trial. A meta-analysis done by Smits suggests that the short allele of the SLC6A4 gene is related to unfavorable response to SSRIs in Caucasian populations. In addition to polymorphisms closely related to individual compounds, the cytochrome P450 superfamily of drug-metabolizing enzymes have polymorphic alleles that affect the efficacy of numerous pharmacological agents, including most antidepressants. Knowledge of a patient's genotype for several of these genes might predict response to a particular pharmacological treatment, a consideration that gains importance when considering the large effect that depression has on outcome after stroke.

Brain stimulation therapy—Several forms of brain stimulation have been used to enhance plasticity after stroke; these include rTMS, tDCS, and direct electrical stimulation. With the use of rTMS in depression, researchers have found that rTMS helps ameliorate depression symptoms in individuals with the BDNF Val/Val genotype more than in those with the Val/Met or Met/Met alleles. In rats, rTMS has been found to modulate expression and function of monoamine transporter proteins. Further studies are needed to understand the molecular mechanisms underlying effects of brain stimulation in order to identify those genes whose variation might impact therapy effects.

Less Studied Genetic Factors for Future Consideration

There are numerous growth factors, signaling pathways, receptors, and other proteins that play a role in the many events related to cortical plasticity. Theoretically, mutations in the genes for any of these factors that alter function or availability of recovery-related proteins might have an effect on cortical plasticity and recovery of function. Two highly studied polymorphisms that have established effects on plasticity-related molecules were described previously. Other potentially important factors are considered below.

NT-3

In addition to BDNF, neurotrophin 3 (NT-3) is highly expressed in neural structures, and a polymorphism in the NT-3 gene has been associated with schizophrenia. The gene has not been studied in the context of stroke, but if it affects function enough to influence schizophrenia risk it may affect plasticity as well.

NTKR

Polymorphisms in the neurotrophic tyrosine kinase receptors (NTKRs) have been studied in the context of Alzheimer's disease. These are the receptors for BDNF and other neurotrophic factors, so polymorphisms that alter their efficacy may produce some of the same changes seen with the BDNF polymorphism.

COMT

The enzyme catechol-O-methyl transferase (COMT) is responsible for catabolizing catecholamine neurotransmitters such as dopamine and norepinephrine and has the highest affinity for dopamine. The gene for COMT has one highly studied SNP, a valine to methionine amino acid substitution at position 108 in the soluble form and 158 in the membrane-bound form (val^{108/158}met). Substituting Met at position 108/158 results in a protein with three to four times lower enzymatic activity and thus higher baseline CNS dopamine levels. This polymorphism in the COMT gene has primarily been studied in the context of working memory and has been associated with risk and therapeutic interventions in schizophrenia. Participants with the low activity Met allele, and thus higher levels of PFC dopamine, exhibit superior performance on working memory tasks, and administering amphetamines to increase CNS dopamine shows differential results based on genotype. In patients with psychosis, cognitive deterioration was the greatest in patients with the Val/Val genotype, intermediate in patients with Val/Met, and the least in patients with the Met/Met genotype. The COMT Val/Val genotype is also associated with motor impairments in patients with severe deficit schizophrenia, giving it at least one direct link to motor performance. Two longitudinal studies have associated the Val/Val genotype with greater cognitive decline with aging, a potentially important finding considering the late age of onset for stroke. Such biochemical and behavior-related studies demonstrate that CNS dopamine levels are increased with the Met allele, enough to see several behavioral effects, which may be a factor in plasticity and rehabilitation.

Cholinergic polymorphisms

Luria, a founder of modern neuropsychology, concluded that cholinergic drugs had a favorable effect on brain repair. The activation or blockage of cholinergic receptors has been shown to influence LTP administration in several paradigms. Administration of scopolamine or other muscarinic acetylcholine receptor antagonists has been shown to impair memory performance in several domains, and administration of nicotine or nicotinic acetylcholine receptor agonists enhances memory and memory-related tasks (and see Giocomo for detailed review). There are several cholinergic receptor SNPs that are beginning to be studied in relation to a variety of neurological conditions. These polymorphisms may represent a future direction to take in the study of genetic factors in brain plasticity.

DYT1

A DYT1 SNP is related to abnormally excessive plasticity to the point of dystonia. Future studies might examine the effects of this SNP in the context of brain repair.

UCHL1

Ubiquitin carboxyl-terminal hydroxylase (UCHL) is an enzyme highly expressed in neurons and is part of the ubiquitin proteasome pathway. UCHL proteins have been shown to be necessary for long-term facilitation in *Aplysia* and hippocampal-dependent memory in rats. The UCHL1 gene in humans contains an SNP that affects its enzymatic activity and might be evaluated in future studies of stroke recovery.

Many of these polymorphisms have undergone little or no study in the context of stroke recovery, but evidence suggests these might be potential avenues for research into genetic effects on plasticity and rehabilitation.

Conclusions

The above findings suggest that genetic factors are important considerations in the context of recovery from stroke, both spontaneous and therapy-induced. Genetic factors may work directly to influence plasticity, or they may modulate other processes that then more directly influence plasticity.

A key question in these studies is how this information can be used to improve patient outcomes. As described previously, such data might be used to design new therapies taking advantage of molecular insights, predict treatment response for individual patients, improve efficiency of resource utilization, and inform entry criteria in clinical trials. Pharmacogenetic approaches will become increasingly popular as SNPs are discovered that modulate drug response. Once effects of single genes are understood, the impact that multiple genes have can be studied.— As always, genetic data must be treated with the highest of ethics and respect. Genetic studies show great promise in explaining and enhancing plasticity and recovery of function after stroke. As rehabilitation techniques become more and more refined, genetics will likely play a larger role in determination of treatment strategies.

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