

Genetic Influences on Neural Plasticity

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Abstract: Neural plasticity refers to the capability of the brain to alter function or structure in response to a range of events and is a crucial component of both functional recovery after injury and skill learning in healthy individuals. A number of factors influence neural plasticity and recovery of function after brain injury. The current review considers the impact of genetic factors. Polymorphisms in the human genes coding for brain-derived neurotrophic factor and apolipoprotein E have been studied in the context of plasticity and stroke recovery and are discussed here in detail. Several processes involved in plasticity and stroke recovery, such as depression or pharmacotherapy effects, are modulated by other genetic polymorphisms and are also discussed. 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 a number of forms of central nervous system injury.

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INTRODUCTION

Many forms of acquired brain injury, such as stroke, along with other neurological diseases and disease conditions, result in a wide range of functional deficits and levels of ability. Even within individuals having very similar injury, recovery and response to therapy can be vastly different. Stroke is the leading cause of serious, long-term disability in the United States, with more than 75% of stroke survivors experiencing disability severe enough to affect employment, and 80% experiencing motor impairments requiring rehabilitation [1,2]. Although motor rehabilitation therapy is recommended after many forms of neural injury, results of this therapy are highly variable between individuals. Understanding factors related to motor recovery, neurological disorders, and pharmacological and therapeutic response could increase the efficacy of motor rehabilitation strategies and dramatically improve quality of life for many.

Successful motor recovery requires plasticity in many areas of the brain. Neural 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. Throughout the early phases of stroke and rehabilitation, neural networks are gradually restored to some degree around the lesion itself, whereas secondary brain regions in a distributed network often are recruited to progressively compensate for and, depending on the extent of damage to a given region, 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 [3-7]. These cortical plasticity events occur in many different forms, from synaptic plasticity at the cellular level to representational map plasticity at the systems 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 to normal 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 such as age can each affect the extent and rate of recovery [8,9], the underlying neural mechanisms in individual subjects often remain incompletely understood.

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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 plasticity-related components could thus influence each individual's capacity for brain plasticity and could explain some of 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 recovery from brain injury. Furthermore, genetic differences might 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, possibly including genetic measures, and the relationship that these factors have with 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, in turn, can be manifested at the systems level as alterations in neural networks and 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 [10]; calcium channel regulation [11]; changes in *N*-methyl-D-aspartic acid (NMDA) receptors [12]; or changes in α -amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA) receptor trafficking [13]. 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 2 neurons that can result from application of high-frequency stimulation to a presynaptic excitatory pathway [14].

These cellular events can be influenced by experience and environment [15], for example, complexity of the housing environment [16,17], maze training [18], avoidance conditioning [19], and sensitization [20]. The mechanisms by which experience and environment exert their influence include increased protein and RNA synthesis [21-24]. Access to such molecular/cellular data can be very difficult in human beings, but this issue can be approached by considering the genetics of such syntheses, matched by physiological and human brain mapping approaches.

Systems plasticity across neural networks in human beings can be studied with a number of methods. Common examples include fMRI, positron emission tomography (PET), electroencephalography, magnetoencephalography, transcranial magnetic stimulation (TMS), or

transcranial direct current stimulation (tDCS). These techniques have been used to study the dynamics of brain systems, such as representational map size, area and magnitude of task-related activation, and changes in activation patterns with time or therapy, as well as neurophysiological measures such as short-interval cortical inhibition, intracortical facilitation, and paired associative stimulation [25-29]. One example of a probe useful for assessing plasticity in human subjects is the motor map, which can be evaluated, for example, by the use of TMS to measure the motor-evoked potential in 1-cm increments along a grid placed over the scalp. The map can then be reassessed after an intervention to measure short-term plasticity [30]. 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. After training, TMS stimulation of this same site results in more evoked thumb movements in the direction of training [27].

Neural plasticity of cortical representational maps can be directly evaluated in animals, across a wide range of motor and sensory domains [31,32]. A key method for its measurement has been intracortical microstimulation [33-36]. In monkeys, sensory maps for the digits have clear boundaries, and those boundaries change with tactile behavioral training or surgical syndactyly [37,38]. Similar maps can be made to examine movement representations in primates and rats; changes in these motor maps are highly specific to the trained skill and are accompanied by an enhancement in performance on the trained task and increased synaptogenesis [33,35]. Studies in animals also suggest that motor map plasticity is characteristic of, and may be crucial to, rehabilitation success after stroke [39].

In human beings, a number of methods have been used to study cortical map plasticity after stroke, including TMS, fMRI, and PET. 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 human beings have been reviewed elsewhere [8,40-43].

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 after stroke. Because many of the neural signals driving plasticity involve the activation of specific genes, genetic variation in human beings might influence the expression of these plasticity-related events and thus their impact on reducing disability in human beings after stroke.

GENETIC FACTORS AFFECTING PLASTICITY

Either directly or indirectly, genetic factors can 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 [8,44-46].

The human genome has a number of polymorphisms, or common and different versions, for genes that influence plasticity through diverse mechanisms. This genetic variation could allow identification of markers that might predict an individual's capacity for brain plasticity and thus potential for recovery after CNS injury such as stroke. Knowledge of such markers might someday allow investigators (1) to study the biological role of a protein via polymorphisms that alter its availability or efficacy, (2) to design novel treatments based on experimentally manipulating the activity of a protein in a similar way that a gene variant does endogenously, (3) to predict which patients would be most likely to benefit from such interventions based on the presence or absence of these polymorphisms, and (4) to identify biologically distinct subpopulations prospectively, which might be of particular value to clinical trials. Two specific candidate genes toward these goals are considered: (1) a single nucleotide polymorphism (SNP) on the gene for human brain-derived neurotrophic factor (BDNF); and (2) the pair of SNPs on the gene for apolipoprotein E (ApoE), resulting in the gene variants $\epsilon 2-4$. In addition to these genes, several less studied but potentially important genetic polymorphisms will be explored.

Brain-Derived Neurotrophic Factor

BDNF, the most abundant growth factor in the brain, affects neural plasticity both directly, through its modulation of cellular processes, and indirectly, through its modulation of other factors that influence plasticity. Its direct involvement will be discussed next, and indirect involvement in a subsequent section.

BDNF is directly involved in plasticity through both short- and long-term influences [47-49]. Shortly after being released, BDNF can rapidly depolarize postsynaptic neurons and elicit short-term postsynaptic effects on ion channels and NMDA receptors [50], in addition to potentiating excitatory synaptic transmission by promoting presynaptic neurotransmitter release [51-53]. In the long term, BDNF can induce lasting changes in synaptic plasticity, neurotransmitter and neuropeptide production, and excitability [54-61]. BDNF is crucial in development and plays an important role in adulthood as well by doing the following: modulating neuronal structure, function, and survival; enhancing synaptic transmission; facilitating LTP; and mediating use-dependent plasticity [62-65].

Decreased BDNF levels in the brain have been associated with numerous functional deficits, providing further insight into the role of BDNF in the brain. Inhibition of BDNF via gene knockout or infusion of antisense BDNF impairs spatial learning and memory in rodents [66-70], and blocking BDNF in the hippocampus erases the cognitive benefits of exercise [71]. BDNF-heterozygote mice fail to form new synapses or modify the balance between excitatory and inhibitory synapses in the somatosensory cortex after 24 hours of whisker stimulation, whereas control mice undergo these structural changes [72]. 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 [73,74]. Subsequent application of exogenous BDNF in the motor cortex can partially restore motor skill acquisition and motor cortical movement representation [74]. These observations emphasize the role of BDNF in modulating the functional organization of the cortex and its clear involvement in processes supporting neural plasticity.

BDNF levels can increase in relation to a number of experimental and environmental stimuli, and this up-regulation is often region specific. In rats, spatial learning and contextual fear conditioning both increase BDNF mRNA and protein in the hippocampus [69,75-77], whereas amygdala-dependent fear conditioning increases BDNF mRNA in the amygdala [78]. BDNF levels are increased in the motor cortex after motor skill learning [79], and whisker stimulation results in enhanced BDNF mRNA expression in barrel fields corresponding to the stimulated whisker [80]. Similarly, monkeys undergoing motor learning show motor map reorganization associated with region-specific up-regulation of BDNF expression, suggesting that BDNF is capable of altering cortical connections at a very specific level in response to experience [81,82]. These studies emphasize the specificity of stimuli and spatial effects in the influence of BDNF on the CNS.

BDNF is also important to many forms of plasticity in relation to repair of neurological conditions [83-86]. BDNF levels have been associated with CNS repair in several rodent stroke models [87-92]. Treatment with exogenous BDNF is associated with better motor recovery [93]. These findings suggest that the plasticity-related effects of BDNF extend to 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 (Val) to methionine (Met) at codon 66 of the BDNF protein (val⁶⁶met). Approximately 30% to 50% of the population is either heterozygous (Val/Met) or homozygous (Met/Met) for this BDNF val⁶⁶met polymorphism [94]. Although this polymorphism does not affect protein function or constitutive release, the intracellular trafficking of BDNF is dramatically altered,

reducing neuronal activity–dependent BDNF release by 25% [95,96].

The val⁶⁶met polymorphism has been associated with abnormal cortical morphology as well as behavioral changes. For example, structural MRI studies of healthy human beings have linked the Met allele with reduced volume in the prefrontal cortex, hippocampus, parahippocampal gyrus, caudate nucleus, and temporal and occipital gray matter [97–102]. These differences may be related to the role of BDNF in development, to effects of continued plasticity throughout the lifespan, or both [103,104]. Volumetric differences could arise through any combination of changes, including decreased dendritic complexity, fewer neuronal and supporting cells, 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. This has been demonstrated for carriers who have either 1 copy (Val/Met) or 2 copies (Met/Met) of this polymorphism. With the use of a battery of neuropsychological tests, Met carriers, as compared with noncarriers (Val/Val), have been shown to have poorer performance on episodic memory tasks, which are more hippocampal dependent, with no differences on tasks that are considered to be less hippocampal dependent, such as semantic memory and verbal fluency [95,97,105,106].

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 [25,28].

Kleim et al [28] investigated how the BDNF val⁶⁶met polymorphism influences network-level plasticity in the motor cortex. They used TMS to study the motor cortex representational map for a hand muscle before and after short-term motor practice. Whereas Val/Val, Val/Met, and Met/Met subjects showed similar motor map organization at baseline, Met carriers exhibited reduced short-term, experience-dependent plasticity in the motor cortex. Similarly, McHughen et al [107] examined the effect of the BDNF val⁶⁶met polymorphism on the same short-term experience-dependent plasticity paradigm by using fMRI and found similar results in multiple regions throughout the brain. Further concurrent evidence across several plasticity-inducing paradigms comes from a TMS study by Cheeran et al [25]. Given the importance of cortical reorganization in the motor system after stroke, these studies suggest that this polymorphism might affect poststroke recovery, although studies of polymorphism effects on long-term plasticity are needed.

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 [53], traumatic brain injury [86], spinal cord injury [83], and Alzheimer disease (AD) [108]. The Met allele has been associated with poorer outcome after subarachnoid hemorrhage [109]. This finding raises the concern that if the 30% to 50% of human beings [94] carrying at least 1 Met allele have abnormal BDNF release and responsiveness, these individuals might have decreased CNS repair and thus diminished capacity for functional recovery after neurological insult.

It is clear from studies in both animals and human beings 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.

Apolipoprotein E

ApoE is primarily involved in lipid transport from 1 cell type or tissue to another, although it also plays a significant role in the growth and regeneration of peripheral and CNS tissues and in modulating neuronal repair, remodeling, and protection [110,111]. There exists a set of 2 common SNPs on the human *ApoE* gene, 1 SNP at amino acid position 112 and 1 SNP at position 158, which result in 3 distinct alleles, termed ϵ 2-4 or ApoE2-4. The most common allele, ϵ 3, has a cysteine residue at position 112 and an arginine at position 158; ϵ 2 has a cysteine at both positions, and ϵ 4 has an arginine at both positions [110]. The most common genotype, E3/E3, ranges in frequency between 43% and 74% of human beings depending on ethnicity [112]. 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 [112,113].

The ApoE alleles are often studied in the context of AD. The ApoE4 allele is highly implicated in the risk for AD, with individuals carrying 1 or more ApoE4 alleles being much more likely to have AD and to have an earlier age of onset as well [114,115]. One theory of the involvement of ApoE in AD is that ApoE3 facilitates the clearing of A β plaques and tangles at a much greater rate than ApoE4 [110]. Expanding beyond this, other investigators have shown that the ApoE4 allele is linked to accelerated cognitive decline with age [116], impaired episodic memory [117], decreased hippocampal volume and cortical thickness [118–120], and memory, cognitive, and attentional impairments on other measures [121,122] (for review, see Parasuraman et al [123]). In addition, individuals carrying the ApoE4 allele have shown fMRI and PET activation patterns similar to patients diagnosed with AD [124,125].

Studies in animal models and cell culture suggest that ApoE is also important in CNS plasticity. Levels of the ApoE protein spontaneously increase after olfactory bulb

lesion [126], and ApoE knockout mice show delayed and diminished synaptic recovery after olfactory bulb lesions compared with wild-type mice [127]. Recent evidence has shown that ApoE4 results in less NMDA receptor activation in response to Reelin signaling, a potential mechanism for its affect on synaptic plasticity [128]. After entorhinal cortex lesions transgenic mice expressing human ApoE4 have substantially less compensatory sprouting and reactive synaptogenesis than those mice expressing human ApoE3 [129]. In human neuronal cell cultures, adding nerve growth factor plus ApoE3 enhances neurite outgrowth, whereas nerve growth factor plus ApoE4 does not [130]. A study of postmortem human brains from patients with AD found that ApoE4 allele carriers show greater levels of neuronal loss than those lacking ApoE4, and impaired neuronal remodeling. This study also found a gene-dose effect, with the greatest levels of neuronal loss occurring in E4/E4 individuals [131].

These data related to ApoE genotype effects on brain morphology and cognitive function suggest that this polymorphism might also affect neural plasticity after brain injury. Studies examining the relationship between ApoE genotype and outcome after severe traumatic brain injury (TBI) support this. In a prospective cohort study, Teasdale et al [132] found that patients with the ApoE4 allele were more than twice as likely to have an unfavorable outcome 6 months after TBI as were patients 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 after TBI [133]. Another meta-analysis found an effect of ApoE genotype on outcome after subarachnoid hemorrhage, but no overall influence on death or dependency in the 3 months after other forms of stroke [134]. In a recent study of 241 patients with stroke followed as part of a clinical trial, investigators found that ApoE genotype was associated with degree of recovery at both 1 and 3 months after stroke, with ApoE4 associated with poorer outcome [135].

Although the relationship between the ApoE polymorphism and poststroke plasticity has received limited study in human beings, 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 human beings.

GENETIC INFLUENCES ON OTHER PLASTICITY-RELATED PROCESSES

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 [136]. Furthermore, learning is often a key component of poststroke therapy [137,138]. As discussed thus far in this review, the BDNF val⁶⁶met and ApoE ϵ 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 [139].

Attention to Task

One key moderator of plasticity is attention and task salience [44]. This is seen in both animals and human beings, across all motor and sensory systems. Animal studies have found that reward modulates attentional valence and influences plasticity [140], and in human beings the paired associative stimulation TMS paradigm elicits plasticity only when the subject is paying attention to the paired stimulus [141]. 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 each been linked to attention. Several studies of children with attention-deficit/hyperactivity disorder (ADHD) have generated evidence that the dopaminergic system and polymorphisms affecting it are involved in attention modulation. Inattention is a hallmark symptom of ADHD, and tests of attention can be used as endophenotypes [142-150].

Another gene recently associated with inattention is the X-linked steroid sulfatase gene. Deletion of this gene results in a greater likelihood of ADHD, particularly the inattentive (nonhyperactivity) subtype. Recently 2 polymorphisms on the gene have been associated with ADHD in children having the combined or inattentive subtype [151].

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 [152], and ApoE genotype has been shown to modulate attention in healthy middle-aged individuals [153].

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 may 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 during their lifetime, but anywhere

from 20% to 79% of stroke survivors [154,155]. Stroke survivors with concurrent depression show worse functional recovery and are 3.4 times less likely to survive the first 10 years after stroke [155,156]. Several factors might influence poststroke depression, including age of onset, gender, lesion location, social support, psychiatric history, stroke severity, and functional outcome [155], but genetics are likely influential 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 [154,157].

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 related to a deficiency in serotonin or norepinephrine because presently the most effective antidepressant drugs act by increasing their levels in the CNS [158]. One key polymorphism, termed 5-HTTLPR, is found in the serotonin transporter gene SLC6A4 and occurs in either a “long” or “short” form [154,157,159]. The short form, which arises from a 44-bp deletion, results in less serotonin transporter synthesized and therefore reduced uptake in the presynaptic neurons [159]. Investigators 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 [154,157,159]. Polymorphisms in interleukin genes have been associated with nonremission, emotional processing, and response to pharmacological agents in subjects with depression [160,161].

The final impact of these genetic studies on understanding and treating depression is not clear at this time, however, because there are also many negative studies. In the 1953-patient Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, 768 SNPs were examined for their relationship to major depression, and only 1 SNP in the gene for serotonin receptor 2A was significantly associated with treatment response [162].

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 [163]. Geriatric depressed Taiwanese and American subjects have been shown to have a greater incidence of the Met allele [164,165], but this association was not replicated in either Chinese [166,167] or German populations [168]. Frodl et al [101] suggested that the lower hippocampal volumes associated with Met allele carriers might make these individuals more susceptible to depression, consistent with the observed reduction in postmortem BDNF levels within the hippocampus and prefrontal cortex of depressed patients [169]. In addition, 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, suggesting that treatment strategies may differ between the 2 groups [170].

Type of Therapy

Exercise Therapy. Therapy including exercise would take advantage of the positive relationship among exercise, BDNF, and brain plasticity. Exercise increases BDNF mRNA and protein in cerebral cortex, cerebellum, and spinal cords of rodents [76,171-173], sometimes in as little as 30 minutes [174]. In human beings with spinal cord injury, multiple brain regions show activity-dependent increases in BDNF levels after 10 to 30 minutes of activity [175]. Because exercise has been shown to up-regulate BDNF, addition of 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 [176,177]. 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 [178]. Drugs studied include the following: the selective serotonin reuptake inhibitors escitalopram, fluoxetine, and citalopram [179-183]; the norepinephrine reuptake inhibitors maprotiline and reboxetine [179,184]; and catecholamine enhancers such as amphetamine [185], levodopa [186,187], and methylphenidate [188]. 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 et al [139] 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 the section “Catechol-O-Methyl Transferase”). Amphetamine improved performance in Val/Val subjects but degraded performance in subjects carrying at least 1 Met allele. Another drug used in the context of stroke recovery is methylphenidate [188], and a polymorphism in the dopamine transporter protein has been shown to affect TMS response to methylphenidate in children with ADHD [189,190].

In a similar manner, several serotonin-related genes have been studied for their effects on response to fluoxetine and citalopram. Peters et al [191] found that polymorphisms and SNP haplotypes in genes for the enzyme tryptophan hydroxylase, the serotonin transporter protein, and serotonin receptor genes, each predicted response to fluoxetine, although these same polymorphisms had no effect on citalopram response in the large STAR*D clinical trial [192]. In a meta-

analysis, Smits et al [193] suggest that the short allele of the SLC6A4 gene is related to unfavorable response to selective serotonin reuptake inhibitors in Caucasian populations. Robinson et al found an improvement in post-stroke depression outcome with escitalopram versus placebo; genetic modulators of escitalopram are being explored [161,182,194]. 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 [195]. 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.

An interesting report has been written regarding the use of warnings from the Food and Drug Administration to indicate that individuals with certain genotypes respond differently to the antiplatelet medication clopidogrel [196]. This report discusses this specific example as well as general topics related to the field of pharmacogenetics.

Brain Stimulation Therapy. Several forms of brain stimulation have been used to enhance plasticity after stroke; these include repetitive TMS (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 [170]. In rats, rTMS has been found to modulate expression and function of monoamine transporter proteins [197]. Further evidence reveals that, in animals, DCS promotes LTP by enhancing BDNF release, and it is likely that, in human beings, tDCS acts in a similar manner [198]. This study found that both tDCS and BDNF Val/Val genotype were significantly associated with enhanced motor learning, although the genotype*tDCS interaction was nonsignificant. Further studies are needed to understand the molecular mechanisms underlying effects of brain stimulation to identify those genetic variations that might impact therapy effects.

Robotic Therapy. Robotic devices have the potential to promote plasticity and improve function in many neurological domains [199-201]. One potential therapeutic implication of this treatment approach in the context of genetics lies in modulating attention, a key covariate in this context. Robotic therapy can combine therapeutic maneuvers with highly salient virtual reality games and other modifiers of attention [202]. Such manipulation of attention might be useful to overcome the effects that certain polymorphisms have on the function of brain attentional systems during therapy.

LESS-STUDIED GENETIC FACTORS FOR FUTURE CONSIDERATION

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

Neurotrophin 3

In addition to BDNF, neurotrophin 3 is highly expressed in neural structures [203], and a polymorphism in the *neurotrophin 3* gene has been associated with schizophrenia [204,205]. The gene has not been studied in the context of neural plasticity; but if studies find that it is a functional SNP, it may affect plasticity as well.

Neurotrophic Tyrosine Kinase Receptors

Polymorphisms in the neurotrophic tyrosine kinase receptors have been studied in the context of AD [206]. 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.

Norepinephrine Transporter Protein

There is evidence that norepinephrine is involved in synaptic plasticity, particularly in the amygdala [207]. There are polymorphisms in the norepinephrine transporter protein (NET) that have been studied in the context of depression, with some positive and some negative results [208]. In addition, the NET protein has a high affinity for dopamine and may affect attention and depression as well [209]. Given the potential effectiveness of amphetamines in stroke recovery [185,210], NET polymorphisms might be explored in the context of stroke recovery and amphetamine therapy.

Catechol-O-Methyl Transferase

The enzyme COMT is responsible for catabolizing catecholamine neurotransmitters such as dopamine and norepinephrine, although it has the highest affinity for dopamine [211,212]. 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) [213]. Substituting Met at position 108/158 results in a protein with 3 to 4 times lower enzymatic activity and thus greater baseline CNS dopamine levels [212,214]. This polymorphism in the *COMT* gene has been

associated with risk and therapeutic interventions in schizophrenia [139,215-218]. Participants with the low-activity Met allele, and thus greater levels of prefrontal cortex dopamine, exhibit superior performance on working memory tasks [213], and administering amphetamines to increase CNS dopamine shows differential results based on genotype [139]. In patients with psychosis, cognitive deterioration was greatest in patients with the Val/Val genotype, intermediate in patients with Val/Met, and least in patients with the Met/Met genotype [219]. The COMT Val/Val genotype is also associated with motor impairments in patients with severe deficit schizophrenia [220], 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 [221,222]. 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

Alexander Luria, the founder of modern neuropsychology, concluded that cholinergic drugs had a favorable effect on brain repair [223]. The activation or blockage of cholinergic receptors has been shown to influence memory and LTP in several paradigms [224-226]. Administration of scopolamine or other muscarinic acetylcholine receptor antagonists impairs memory performance in several domains [227-230], and administration of nicotine or nicotinic acetylcholine receptor agonists enhances memory and memory-related tasks [231-235] (see Giacomo and Hasselmo [236] for a detailed review). There are several cholinergic receptor SNPs that are beginning to be studied in relation to a variety of neurological conditions [237-239]. 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 [240]. Future studies might examine the effects of this SNP in the context of brain repair.

Ubiquitin Carboxyl-Terminal Hydroxylase-1

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 [241,242]. The *UCHL1* gene in human beings contains an SNP that affects its enzymatic

activity [243] 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.

CONCLUSION

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

A key aspect of these studies is how patient outcomes may benefit from this information. 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 use, and inform entry criteria in clinical trials. Pharmacogenetic approaches will likely receive increased attention as stronger evidence accrues supporting a role of SNPs in modulating drug response. Once the effects of single genes are understood, the impact of multiple genes or epigenetic phenomena can also be studied [244-246]. As always, genetic data must be treated with the greatest of ethics and respect. Genetic studies show great promise in explaining and enhancing the potential of plasticity and recovery of function after neural injury such as stroke. As rehabilitation techniques become more and more refined, genetics will likely play a larger role in determination of treatment strategies for individual patients.

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