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The influence of genetic factors on brain plasticity and recovery after neural injury

Kristin M. Pearson-Fuhrhop^a, Erin Burke^a, and Steven C. Cramer^{a,b}

Purpose of review

The fields of clinical genetics and pharmacogenetics are rapidly expanding. Genetic factors have numerous associations with injury and with treatment effects in the setting of neural plasticity and recovery.

Recent findings

Evidence is reviewed that established genetic variants, as well as some more recently described variants, are related to outcome after neural injury and in some cases are useful for predicting clinical course. In many cases, the interaction of genetics with clinical factors such as experience and therapy may be important. As an extension of this, genetic factors have been associated with differential response to a number of forms of therapy, including pharmacological, brain stimulation, psychotherapy, and meditation. Genetic variation might also have a significant effect on plasticity and recovery through key covariates such as depression or stress. A key point is that genetic associations might be most accurately identified when studied in relation to distinct forms of a disorder rather than in relation to broad clinical syndromes.

Summary

Understanding genetic variation gives clinicians a biological signal that could be used to predict who is most likely to recover from neural injury, to choose the optimal treatment for a patient, or to supplement rehabilitation therapy.

Keywords

genetics, plasticity, recovery

INTRODUCTION

Recent years have seen substantial investigation into the relationship between genetic factors and disease pathogenesis and treatment efficacy, as well as, specifically, features of neural plasticity. In several cases, findings have been reliably replicated, for example, the association of the apolipoprotein (ApoE) E4 allele with Alzheimer's disease, dopamine variants with schizophrenia and working memory, serotonin polymorphisms with depression, and brain-derived neurotrophic factor (BDNF) with cortical plasticity. Many more have been studied, often with less consistent results. Although genetic factors alone rarely have a major effect on clinical state, such data may be useful in some cases to improve clinical decision-making.

FORMS OF GENETIC VARIATION

Genetic variation takes several forms and can be studied in many ways. A gene may be altered by one nucleotide, which may result in an amino acid change in the protein, or in altered transcription or translation efficacy if the nucleotide change occurs

in a promoter region. Alternately, a segment of the gene may be repeated, or a nucleotide may be inserted or deleted. A genetic mutation is a form of genetic variation that is rare in the population and that causes significant functional alteration. Examples include the single nucleotide mutation that causes sickle cell anemia, or the CAG repeats found in Huntington's disease. When a genetic variation occurs commonly and has a relatively small effect on behavior or phenotype, it is termed a polymorphism. A polymorphism may be a single-nucleotide polymorphism (SNP), a variable number of tandem repeats (VNTR), or an insertion/deletion polymorphism.

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KEY POINTS

- Several genetic factors predict the level of recovery following neural injury.
- Genetic factors have been associated with response to various forms of treatment, including pharmacology, psychotherapy, drug side effects and meditation.
- The association that genetic factors have with outcome and with response to therapy might interact with a number of clinical factors such as experience, therapy, or sex.
- Genetic associations might be most accurately identified when studied in relation to distinct forms of a disorder rather than in relation to broad clinical syndromes.
- Genetic factors might be associated with differences in the neural signals obtained with neuroimaging techniques such as TMS or fMRI.

The most common approach to studying the impact of genetic variation to date has been to study single polymorphisms and their association with disease, or with an endophenotype such as brain function. A candidate gene approach may be used in this context in which a polymorphism is chosen *a priori* based on its likely association with the condition of interest. Alternately, a genome-wide association study (GWAS) may be done, during which all known polymorphisms, or some massive number of them, are assessed [1[■]]. Another approach utilizes a gene score that sums the effects of multiple polymorphisms in the same system [2,3,4[■],5[■]]. Other approaches include examination of exome sequencing, epigenetics, and epigenomic and transcriptomic variation [6[■]].

MEASUREMENT OF BRAIN PLASTICITY IN HUMAN PATIENTS

After neural injury, significant reorganization of brain networks occurs to a variable extent and can be associated with substantial behavioral recovery. Animal studies have provided important insights into the mechanisms of this plasticity, with molecular and cellular findings based on direct examination of neural tissue. These molecular studies are of pivotal significance, for example, for selecting polymorphisms to investigate and for interpreting results of human genetic studies. In human patients, direct molecular study of tissue is rarely available. Noninvasive neuroimaging methods are, therefore, employed to understand nervous system structure and function. Clinical neuroimaging also facilitates

our understanding of plasticity mechanisms elucidated in animal models of injury, as well as the plasticity that occurs with subsequent treatment [7].

A number of approaches to neuroimaging have been pursued in the study of plasticity. A prime example is functional MRI (fMRI), which has very good spatial resolution, but temporal resolution can be limited, and the blood oxygenation level-dependent (BOLD) contrast often used in fMRI studies is vulnerable to effects of vascular disorder, altered cerebral blood flow (CBF), and head motion. MRI techniques can also be used to study CBF, network connectivity, white matter integrity, tractography, and more. Positron emission tomography (PET) measures brain activation, as well as CBF, metabolism, neurochemistry, receptor kinetics, and more. However, PET involves some exposure to ionizing radiation, temporal resolution is generally low, and many forms of investigation require proximity to a cyclotron. A method receiving increased attention to study brain function and plasticity is dense array electroencephalography. Although this method examines signals from only the cerebral cortex and has some limitations in spatial resolution, the technique provides excellent temporal resolution, it is relatively tolerant to patient movement, it carries a low cost, and it can be easily implemented in complex clinical settings. Transcranial magnetic stimulation (TMS) is a useful probe of neurophysiology, particularly in the motor system. TMS has excellent temporal resolution, but motor-evoked potentials (MEPs) can be difficult to obtain in patients with neural injury, and TMS generally evaluates only a small portion of the cerebral cortex. Other techniques used to study brain plasticity in human patients include single-photon emission computed tomography, near-infrared spectroscopy, and magnetoencephalography. As no single method is sufficient to examine all aspects of neuroplasticity, multiple neuroimaging modalities can be used in order to achieve the most robust understanding [7].

GENETICS OF NEURAL PLASTICITY AND RECOVERY

Various genes have been associated with brain plasticity and recovery from neural injury (for review, see [8]). One highly studied genetic variant is a polymorphism in the gene for BDNF, a growth factor important to many forms of development, plasticity, and repair. A valine is replaced with methionine at position 66, which results in 18–30% less activity-dependent secretion of the BDNF protein [9,10]. Another highly studied genetic variation is in ApoE, which is the most abundant

brain lipoprotein. A combination of polymorphisms results in the ApoE2–ApoE4 genotypes [11], which are associated with differences in several neural repair processes as well as to the risk of Alzheimer's disease. A third major genetic variant is the insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR), which has a 44-bp insertion/deletion, and thus occurs in either a short (s) or long (l) form that modulates expression of the gene. The short form is associated with vulnerability to stress and depression including poststroke depression [12,13]. Several dopamine-related polymorphisms are being studied, including a valine-to-methionine amino acid change at position 108/158 of the catechol-O-methyltransferase (COMT) enzyme. This amino acid change results in a protein with 3–4 times less enzymatic activity, and thus higher synaptic dopamine availability [14]. Variation in these and related genes have been associated with differences in recovery following neural injury.

Several of these polymorphisms have been associated with differences in outcome after neural injury. For example, a study of 255 acute stroke patients found that the presence of the ApoE4 allele and BDNF Met allele were each associated with poorer recovery and greater disability post-stroke [15], similar to prior findings in subarachnoid hemorrhage. In a rehab sample of 648 patients with traumatic brain injury (TBI), ApoE4 genotype predicted long-term functional outcome, with E4 carriers exhibiting worse outcomes 1 year post-injury. Additionally, a gene by sex interaction was seen, as the negative effect of the E4 allele was greater in women than men [16].

The above studies examined recovery, using scales that examine function in a broad sense, but the study of genetics of recovery also benefits from examination of more specific associations. Recovery generally entails change in a complex array of individual brain regions and behaviors. For example, depending on the severity and nature of the injury, successful recovery may necessitate the return of consciousness, language, motor function, mood stability, or cognitive function. The most common consequence of TBI is cognitive impairment in domains such as executive function, memory, attention, impulsivity, and emotional control. Genetic polymorphisms in the genes for COMT and BDNF have been found to influence these processes in healthy individuals, and likely also influence the recovery of these processes after neural injury [17]. In a study including patients with Alzheimer's disease or dementia, the COMT Val allele, associated with lower synaptic dopamine, was associated with reduced gray matter in several dopamine-related

structures [18[¶]]. It is unclear whether the Val allele exacerbates neurodegenerative disorders or whether the Met allele is protective, but the results show that an alteration in the COMT enzyme affects degeneration specifically in dopamine-innervated structures. In a study of patients 1 month following mild nonpenetrating TBI, the BDNF Met allele was associated with slower processing speed [19]. It is important to note, however, that some genetic variants may play a different role in the injured versus healthy brain, or may be specific to one cognitive domain or injury severity. This has been specifically examined for the BDNF Val66Met polymorphism [20[¶]]. A study of patients with penetrating TBI in the chronic phase found that the BDNF Met allele was correlated with improved executive function, compared with the Val allele. [21]. Thus the stability provided by the Met allele may confer some advantage after TBI, in contrast to studies in healthy individuals that find the Val allele provides an advantage through enhanced brain plasticity. Such studies suggest that associations with polymorphisms identified in healthy patients might not directly extend to pathological/clinical contexts such as neural injury.

Many genetic differences are not apparent at baseline but emerge as an interaction with experience and training, or when examined in the long term. This has been suggested in many studies of 5-HTTLPR and with the classic studies of genetic variation in monoamine oxidase-A and antisocial behavior. In the case of ApoE, the E4 allele is associated with long-term functional outcome, but not initial injury severity, following stroke [15] or TBI [16]. This suggests that ApoE influences the neural plasticity related to recovery rather than initial response to injury. Similarly in healthy adults, a dopamine gene score was not related to baseline motor performance but was significantly associated with acquisition of a motor skill [22]. These studies highlight the important point that genetic variation might be maximally apparent when studied in relation to experience. Experience includes acute care, rehabilitation therapy, home life, and many psychosocial factors, and these may differ greatly across various neural afflictions.

IDENTIFICATION OF NEW GENETIC VARIANTS

Other polymorphisms, in addition to commonly studied genetic variants such as BDNF and ApoE, have been implicated in stroke recovery. Some are related to acute injury and its relationship to early repair events. For example, recent evidence suggests an important role of inflammation-related genes in

stroke outcome. Marousi *et al.* [23] found that SNPs in interleukin 4 and interleukin 10 were correlated with likelihood of a recurrent ischemic event and predictive of functional outcome, respectively. Inhibition of the cyclooxygenase-2 (COX-2) gene has been associated with reduced brain injury after stroke in ischemic animal models, and the presence of the COX-2 rs5275C allele and the COX-2 rs20417C allele was associated with better outcome 90 days poststroke [24]. One new polymorphism that may greatly affect stroke recovery and post-stroke plasticity is found in the gene for tissue-type plasminogen activator (t-PA). The t-PA protein, known for its role for acute reperfusion after stroke, is also thought to be highly involved in neurotransmission and cortical plasticity [25]. A study of postmortem human brains found a large difference in t-PA mRNA between carriers of the 7351C and T alleles [26[■]]. Thus far this polymorphism has not been studied for its relationship to cortical plasticity in humans, but evidence from animal and postmortem studies suggests that it might significantly affect poststroke neural plasticity. More research is needed to determine the exact biological consequences of these genetic variations.

GWAS is particularly helpful for identification of new genetic associations [1[■]]. A large GWAS has found and replicated an association of an HDAC9 gene variant with large vessel ischemic stroke [27]. The mechanism is not known, and therefore this association would not have been found with a candidate gene approach. This study also replicated previously discovered associations of gene polymorphisms with specific stroke subtypes, and highlights an important point: genetic associations might be most accurately identified when studied in relation to distinct forms of disorder. Numerous, divergent disease states can produce the clinical syndrome of stroke, but identification of genetic associations might necessitate studying these different disease states separately. The need to consider that a single clinical diagnosis can arise from many distinct pathological states likely extends to other forms of neural injury beyond stroke.

Gene expression studies are also useful for identifying new variants. For many forms of neural injury, there has been limited clinical trial success in pharmacologically improving outcome. There remains a great need to develop novel ways to treat neural injury and its sequelae. One such way is to use gene expression profiling from peripheral whole blood to identify unique gene expression patterns that are associated with neurological diseases/disorders and among their phenotypic subtypes [28]. Evidence from an animal TBI model suggests that gene expression regulation could help monitor

injury progression, and thereby help identify novel protein targets for future pharmacotherapy development [29].

RELEVANCE OF GENETIC POLYMORPHISMS

Knowledge of plasticity-modulating polymorphisms may help predict the natural course of recovery, but the greatest clinical benefit from genetics research might come from identification of polymorphisms in order to guide details of treatment, for example, choice, dose or duration. Such an approach is being used in oncology in which the BRCA1 and 2 mutations are used to direct the management of some patients' breast cancer [30]. Similarly, variations in the CYP2C19 gene, coding for the cytochrome P450 2C19 protein, may be considered when prescribing the platelet aggregation inhibitor clopidogrel [31,32[■],33].

A number of potential opportunities exist whereby genetic factors might influence pharmacotherapy after neural injury. Several drugs are commonly used following neural injury, including the dopamine precursor levodopa, selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs), and acetylcholinesterase inhibitors [34]. Genetic variations have been shown to interact with many of these [8]. One recent study found that the effects of levodopa on skilled motor learning and motor cortical plasticity were modulated by dopamine genetics [22]. SSRIs and SNRIs are given primarily to treat comorbid depression [34], but some studies suggest that they favorably influence rehabilitation as well [35[■]]. The 5-HTTLPR s/l polymorphism, along with others, modulates response to antidepressant drugs in major depressive disorder [36] and may have an impact on SSRI and SNRI response in poststroke depression and rehabilitation. There are genetic variations in drug metabolizing enzymes that have been shown to alter drug responses to a wide variety of pharmacological agents, including most antidepressants [37]. In addition to modulating drug efficacy, genetic variation has been found to influence the likelihood of medication side effects in conditions such as epilepsy [38], diabetes [39], rheumatoid arthritis [40], cancer [41], and depression [36]. The increased likelihood of side effects due to genetic variation will be a consideration during the development of drug treatments for neural injury. Particularly, in conditions when multiple drugs or classes of drugs could potentially be used, pharmacogenetics might shorten the process of finding the best drug for the patient, and thus reduce the number of drugs the patient

must be exposed to before settling on the appropriate treatment [42[■]]. However, several ethical concerns exist including, but not limited to, obtaining informed consent from patients who are not competent, maintaining confidentiality of such sensitive data, and understanding the uncertainty of genetic associations [42[■]].

An understanding of genetic factors might also influence treatment of neural injury through nonpharmacological forms of intervention. For example, several forms of brain stimulation, whereby cortical excitation is focally modulated, are under investigation for the treatment of wide-ranging conditions such as stroke [43–45], Parkinson's disease [46], Alzheimer's disease [47,48], and TBI [49]. Polymorphisms in genes coding for important plasticity-mediating proteins could influence response to such treatment. Polymorphisms in the NMDA NR1 and NR2B subunit genes have been shown to affect TMS-induced cortical excitability and plasticity [50]. Additionally, recent evidence has found a significant positive relationship between homozygosity of the G allele in a common SNP of the transient receptor potential vanilloid 1 channel gene and increased cortical excitability [51[■]]. Many investigators have found differences in experimentally induced motor cortex plasticity between BDNF Val66Met Met carriers and noncarriers. Most recently, Cirillo *et al.* [52] found that individuals homozygous for the BDNF Val allele had greater TMS MEPs following paired associative stimulation (PAS), simple motor training, and complex motor training. Met allele carriers experienced increased MEP amplitude with only the simple motor training task, and Met/Met homozygotes had reduced MEP amplitude with complex motor training. These findings suggest differential cortical plasticity patterns across BDNF genotype groups, and warrant further work studying the effect of BDNF genotype on cortical plasticity and motor task performance in neurologically compromised populations. As methods for modulating cortical excitation receive increased study as a treatment for neural injury, the need to study genetic variants related to neural plasticity will increase. It is likely that plasticity-related genetic variants could differentially affect treatment response.

Although much research has gone into studying the effects of common genetic variants on cortical plasticity, little is known about the effects of SNP interactions. Witte *et al.* [53] studied the combined effects of the BDNF Val66Met and COMT Val158Met polymorphisms on PAS-induced short-term motor cortex plasticity. PAS-induced cortical plasticity was greater in patients that were homozygous for the BDNF Val allele and heterozygous for the COMT Met

allele. These patients also exhibited better implicit learning. Findings from Manso *et al.* [54] suggest that there might be effects of genetic interactions on stroke recovery as well, albeit in the absence of an intervention. They found interactions between three trophic factor SNPs that predicted stroke outcome, although no SNP independently correlated with outcome. Genetic interactions are difficult to study but important to consider.

OTHER FACTORS THAT INFLUENCE PLASTICITY AND RECOVERY

In addition to influencing recovery itself, genetic factors modulate covariates and other processes that are directly involved in recovery such as depression, vulnerability to stress, CBF, and cognitive impairment. Depression has a serious negative impact on stroke recovery [55] and is modulated by several genetic and environmental factors [56,57[■]].

The 5-HTTLPR s/s genotype has been robustly associated with an increased risk for depression [56], including poststroke depression [13]. Studies of this polymorphism with treatment response have found that the s allele, compared with the l allele, is associated with poorer response to antidepressant drugs [36] but improved response to psychosocial therapy [57[■]]. This makes knowledge of a patient's 5-HTTLPR genotype a valuable contributor to the management of poststroke depression. Patients with genetic susceptibility to depression might benefit most from in-person rehabilitation therapy and might also be less likely to comply with self-motivated telerehabilitation.

Stress is a key environmental variable brought on by the recovery process following neural injury. Vulnerability to stress has been found to have a genetic component [56]. Experimental stress paradigms resulted in worse working memory performance for COMT Met/Met homozygotes than COMT Val/Val homozygotes [58,59]. Potentially explaining these results is a study in children that found that the COMT Met allele is associated with a higher cortisol response to stress [60[■]]. Patients experiencing stress following brain injury might include meditation in their daily routine. Animal studies find that the BDNF Met allele confers significant vulnerability to stress [61], and one study suggested that indeed meditation might be more helpful for BDNF Met carriers [62].

CBF is affected by functional variants in the gene for nitric oxide synthase [63], and individuals with such polymorphisms may have a decreased ability to maintain adequate CBF following TBI [64]. Using PET, it has recently been found that the BDNF Val66Met polymorphism increased resting CBF in

the prefrontal cortex and hippocampus [65^{*}]. These results could have important implications if functional imaging methods such as BOLD fMRI or PET CBF are being used to monitor treatment response after neural injury.

CONCLUSION

With numerous studies showing that certain genetic polymorphisms decrease the likelihood of recovery following neural injury, the question becomes ‘what can we do for these groups of patients?’ Pharmacogenetics gives clinicians more information in the search for the best therapy – pharmacological or otherwise – for each patient. Understanding the involvement of genetics in comorbid conditions such as depression can help in treatment or in the prevention of such complications. The ever-increasing knowledge of genetic variants gives clinicians and researchers an important avenue of insight for defining the best treatments following neural injury for individual patients.

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Conflicts of interest

S.C.C. has served as a consultant to GlaxoSmithKline, Pfizer, and Microtransponder.

There are no other conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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