

Genetics as a molecular window into recovery, its treatment, and stress responses after stroke

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ABSTRACT

Stroke remains a major source of adult disability in the USA and worldwide. Most patients show some recovery during the weeks to months following a stroke, but this is generally incomplete. An emerging branch of therapeutics targets the processes underlying this behavioral recovery from stroke toward the goal of reducing long-term disability. A key factor hampering these efforts is the very large degree of variability between stroke survivors. Available data suggest that genetic differences could explain an important fraction of the differences between subjects. The current review considers this from several angles, including genetic differences in relation to drugs that promote recovery. Genetic factors related to physiological and psychological stress responses may also be critically important to understanding recovery after stroke and its treatment. The studies reviewed provide insights into recovery and suggest directions for further research to improve clinical decision-making in this setting. Genetic differences between patients might be used to help clinical trials select specific patient subgroups, on a biological basis, in order to sharpen the precision with which new treatments are evaluated. Pharmacogenomic factors might also provide insights into inter-subject differences in treatment side effects for pharmacological prescriptions, and behavioral interventions, and others. These efforts must be conducted with the strictest ethical standards given the highly sensitive nature of genetic data. Understanding the effect of selected genetic measures could improve a clinician's ability to predict the risk and efficacy of a restorative therapy and to make maximally informed decisions, and in so doing, facilitate individual patient care.

The worldwide burden of stroke disability is high and increasing. In the USA alone, there are >795,000 new strokes each year. Most patients (>90%) survive the acute episode, living an average of 6–7 years thereafter.¹ As a result, there are >7,000,000 adult stroke survivors in the USA,² making stroke perennially among the leading causes of human disability³ and the leading neurological cause of lost disability-adjusted life years.⁴ Indeed, according to a recent American Heart Association Scientific Statement,⁵ stroke ‘continues to represent the leading cause of long-term disability in Americans.’ Consistent with this, persons with stroke represent the largest impairment group of Medicare beneficiaries receiving

inpatient medical rehabilitation services in the USA.^{6,7}

Stroke is a very heterogeneous condition, and many different signs and symptoms may be present and contribute to disability. The most common type of deficits after stroke are motor deficits, present in >80% of patients initially.^{8–11} Motor deficits persist in 55–75% of patients and are associated with reduced quality of life.^{8–11} Since advances in stroke medicine are producing a sharp increase in the fraction of patients surviving the acute stroke, the burden of stroke disability will likely increase in the coming years.¹² Consistent with this, evidence shows that significantly more individuals with stroke reported dexterity and cognitive impairments in 2005 compared with respondents in 1996; similarly, despite medical advances over this interval, quality of life after stroke has not improved.¹³ Reducing disability, particularly through improving motor function, is therefore a critical and time-urgent public health issue.

RECOVERY AFTER STROKE

All patients show spontaneous behavioral improvement during the weeks to months following a stroke; however, in most cases, the degree of improvement is incomplete.¹⁴ A number of interventions, including rehabilitation therapies, pharmacological compounds, and devices, are commonly provided as standard of care during this period, and in some cases during the years that follow. These therapies aim to facilitate neural plasticity and to optimize post-stroke recovery.¹⁵ Rehabilitation therapies include occupational, physical, speech, cognitive, and psychological therapy and aim to support patients as they re-engage in activities of daily living. Pharmacological interventions for enhancing recovery after stroke is an area of practice with few firmly established practices.

A key issue in understanding stroke recovery and its treatment is the enormous degree of inter-subject variability. A major area of research in this field aims to understand the factors that govern these differences. Increasing evidence suggests that genetic variation may provide a window into this issue. Here we provide a review of several key factors relating genetics to post-stroke recovery. Two key areas of focus are genetic factors as they relate



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directly to neural repair, and as they relate to psychological and physiological stress responses.

PHARMACOLOGICAL THERAPY AND NEURAL REPAIR AFTER STROKE

Currently, few drugs are used in the specific setting of neural injury recovery. Whereas reperfusion therapies such as intravenous tPA and clot retrieval devices are approved for treating patients in the initial hours after stroke onset, there are no pharmacological treatments specifically approved to promote neural repair thereafter. Catecholamine-enhancing drugs are occasionally prescribed,¹⁶ and may enhance recovery,^{17–21} but evidence is incomplete and these compounds are not formally approved for this indication. A number of drugs are being studied for their potential to enhance brain plasticity and rehabilitation therapy.²² These include the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram,^{20 21 23–25} the norepinephrine reuptake inhibitor reboxetine,²⁶ dopamine agonists such as L-dopa,^{17–19} amphetamine,^{27–30} methylphenidate,^{31 32} and acetylcholinesterase inhibitors such as donepezil.^{33 34} These drugs are prescribed at each physician's discretion.¹⁶ The clinician's ability to predict the risk and efficacy of different drugs and to make informed decisions about which patients require additional monitoring following drug administration may be improved with a better understanding of the genetic variants that modulate the effect of pharmacological therapies on neural injury recovery. Moreover, a better understanding of how genetic factors contribute to differences in the subject's response to therapy may be useful to inform patient selection, and thus increase statistical power, in clinical trials of such agents.

GENETIC FACTORS AND NEURAL REPAIR

Genetic polymorphisms may impact the course of stroke recovery by reducing an individual's capacity for cortical plasticity (for review, see refs. 35–38). Polymorphisms in the genes for brain-derived neurotrophic factor (BDNF) and apolipoprotein E (ApoE) have been studied most extensively in regard to genetic associations with inter-subject differences in cortical plasticity. BDNF is the most abundant growth factor in the brain and is important to many forms of development, plasticity, and repair. A common³⁹ single nucleotide polymorphism (SNP) in its gene results in a switch from valine to methionine at codon position 66 (rs6265), resulting in 18–30% less activity-dependent secretion of the BDNF protein.^{40 41} This BDNF val⁶⁶met polymorphism has been associated with reduced short-term cortical plasticity in humans by several techniques,^{42–44} with some evidence suggesting that this effect may be overcome with intense training.⁴⁵ Given the importance of cortical reorganization in the motor system after stroke, these studies suggest that the BDNF val⁶⁶met SNP might affect post-stroke recovery. Evidence from studies of patients with stroke is consistent. The presence of this SNP has been associated with poorer outcome after subarachnoid hemorrhage⁴⁶ and with poorer recovery and greater disability post-stroke,⁴⁷ although as in healthy subjects this effect might wane over time post-stroke.⁴⁷ This finding raises the question as to whether the 30–50% of human beings³⁹ who carry this SNP might have a different

biology of stroke recovery, one that would benefit from appropriately tailored rehabilitation and perhaps pharmacological therapy.

ApoE is the most abundant brain lipoprotein, and its gene contains a frequently studied combination of two SNPs that result in three ApoE polymorphisms, termed epsilon2, epsilon3, and epsilon4 polymorphisms. ApoE has been found to play a significant role in the growth and regeneration of peripheral and central nervous system tissues, is involved in modulating neuronal repair,^{48 49} and has been found to substantially affect the risk for Alzheimer's disease.^{50 51} The presence of the ApoE epsilon4 polymorphism has been associated with poorer recovery and greater disability post-stroke⁴⁷ as well as poorer long-term outcome following several other conditions such as traumatic brain injury (TBI).^{52 53} The ApoE epsilon4 polymorphism may therefore represent a genetic factor associated with less effective endogenous repair and recovery following neural injury such as stroke.

Genes in inflammatory pathways may also play an important role in stroke outcome. A SNP in interleukin 10 was found to be predictive of functional outcome following ischemic stroke, and an interleukin 4 SNP correlated with the likelihood of a recurrent ischemic event.⁵⁴ The COX-2 rs5275C and rs20417C alleles were associated with better outcome 90 days post-stroke.⁵⁵ If these associations were replicated, they would suggest potential pathways for individualized medicine in order to boost outcomes among patients who are at risk of poor functional outcome.

Of course, functional outcome is not limited to the motor system. Critical questions remain in relation to level of consciousness, language, attention, mood, and a range of cognitive functions. There is likely to be a substantial overlap with findings from studies of patients with TBI.⁵⁶ In some cases, the function of the gene under study suggests specific therapeutic applications.^{57–59} Further study is needed to understand how these genetic factors may interact with a range of key clinical measures such as extent of brain injury, severity of behavioral deficits and clinical factors such as age.

PHARMACOGENETICS

To date, human studies examining pharmacogenetic factors in relation to neural repair are limited in number. A better understanding of the interaction between key genetic variants and pharmacological interventions would foster more precise individualization of treatment planning. Three examples are considered below.

Dopaminergic drugs

Studies regarding the efficacy of dopaminergic drugs are promising but results to date have been mixed,^{17–19 60} perhaps in part due to the impact of genetic variation for proteins that underlie dopamine neurotransmission. A recent study found that the effects of L-dopa on skilled motor learning and motor cortical plasticity varied in relation to dopamine genetics,⁶¹ using a polygene score to model this complex brain neurotransmitter system. In this study, a gene score was used to sum the individual effects of five genetic variants affecting the dopamine system. Smaller gene scores, corresponding to lower endogenous brain dopaminergic neurotransmission, were associated

with poor motor skill learning on placebo but an enhancement in learning with L-dopa. In contrast, individuals with greater dopamine gene scores, representing higher endogenous brain dopaminergic neurotransmission, showed greater learning on placebo but significant worsening in skill learning after consumption of L-dopa.⁶¹ Similar results have been found using this gene score to study major depression⁶² and impulse control.⁶³ If these results remain true in the stroke population, such genetic information might greatly sharpen the precision with which dopaminergic drugs are prescribed to optimize rehabilitation therapy.

Serotonergic drugs

In stroke care, SSRIs are given primarily to treat comorbid depression,¹⁶ but some studies suggest that such drugs may favorably influence other rehabilitation outcomes as well such as motor and cognitive measures.^{20 21 26} A 44-bp insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) results in a protein that occurs in either a long (l) or short (s) form. Such serotonin polymorphisms may modulate response to antidepressant drugs in major depressive disorder,⁶⁴ although this effect is debated.^{65 66} This SNP may also impact SSRI response when treating post-stroke depression or when using SSRIs to enhance rehabilitation therapy. Given that post-stroke depression worsens functional outcomes,⁶⁷ understanding the pharmacogenetics of antidepressants has great potential to improve many dimensions of care following stroke. A patient's 5-HTTLPR genotype might also inform treatment choice, as the short form of this protein (s allele) is associated with poorer response to pharmacological intervention,^{64 68} better response to psychosocial therapy⁶⁹ and greater sensitivity to social environments.

More generally, genetic variations in enzymes of drug metabolism, such as the cytochrome P450 (CYP) family, have been shown to alter drug responses to a wide variety of pharmacological agents including most antidepressants.⁷⁰ Meta-analysis has also found that SNPs in the genes for BDNF and tryptophan hydroxylase 1 may be associated with differences in antidepressant response.⁶⁴

Cholinergic drugs

Though donepezil is primarily used in the treatment of AD, it has been studied as a potential treatment for aphasia and cognitive impairment following stroke.^{33 34} Polymorphisms in the CYP2D6 gene (rs1065852 and rs1080985) have been associated with donepezil efficacy in AD,^{59 71–73} and one such study also found higher blood plasma concentrations of donepezil with increasing CYP2D6*10 alleles.⁷¹ These findings suggest that a patient with aphasia or cognitive impairment after stroke might benefit from addition of donepezil, particularly if a carrier of the CYP2D6*10 or CYP2D6*41 alleles.

Other considerations

In addition to its modulating effects on drug efficacy, genetic variation may affect the risk/benefit profile of a drug through its influence on the likelihood of medication side effects. In addition to interactions with tPA as discussed above, genetic polymorphisms have been associated

with the altered side effect profile in relation to drugs for vascular disease such as tPA⁷⁴ and clopidogrel,⁷⁵ and in diverse conditions such as epilepsy,⁷⁶ diabetes,⁷⁷ rheumatoid arthritis,⁷⁸ cancer,⁷⁹ major depression,⁸⁰ and Parkinson's disease.⁸¹ The increased likelihood of side effects due to genetic variation might also emerge as a consideration during development of drug treatments to promote neural repair. In particular, when multiple drugs (or classes of drugs) might potentially be prescribed, pharmacogenetics has the potential to shorten the process of finding the best drug for each individual patient, and thus reduce the number of drugs the patient must be exposed to before arriving on the most effective treatment.⁸²

REHABILITATION THERAPY AND STRESS RESPONSES

Stroke is a life-changing experience that can be extremely stressful and potentially traumatizing for individuals. Stroke-related stress can manifest as psychological symptoms, such as depression or post-traumatic stress symptoms,⁸³ and can negatively impact the body's natural physiological functioning.⁸⁴ These stress-induced psychological and physiological responses are important because they may interfere with neural recovery,^{84 85} and may impede the effectiveness of rehabilitative treatments. The degree of psychological and physiological stress following stroke varies across patients. Evidence from prior studies on individuals who have experienced highly stressful or traumatic experiences suggests that genetic variants explain a significant portion of the inter-subject differences in psychological and physiological stress responses.^{86 87} The idea that stress responses may interact with rehabilitation therapy and that genetic variation may be associated with differences in stress responses suggests the need for a better understanding of how stress-related genetic variants might promote—or limit—the effectiveness of various rehabilitation therapies.

GENETICS AND STRESS RESPONSES

Despite strong evidence showing that genetic variants partly explain differences in psychological and physiological stress responses, our understanding of these issues is still in its infancy. Additional research efforts dedicated to investigating the role of genetics in psychological and physiological stress responses following stroke may help identify individuals who are in greatest need, and may most benefit from a larger, or more individualized dose of rehabilitation therapy. Several key physiologic systems that contribute to stress-related health conditions are considered below.

Hypothalamic pituitary adrenal axis

Not surprisingly, much of the research in this area has focused on the hypothalamic pituitary adrenal (HPA) axis, as it is the central brain stress response system. Allostatic load theory highlights the role of physiological load in the health damaging effects of chronic stress and has given rise to an abundance of research linking HPA axis response to health.⁸⁸ This work generally characterizes the HPA axis response to *acute* stress as beneficial in that it mobilizes bodily resources to cope,⁸⁸ and specific SNPs from HPA axis genes (*FKBP5*, *CRHR1*, *NR3C2*) have been identified

as possible candidates for inclusion in a multilocus genetic profile of high-risk stress responsiveness.⁸⁹ HPA axis SNPs also appear to be good candidates for testing gene-environment interactions in relation to indices of well-being.^{87 90}

Endocannabinoid system

The endocannabinoid (ECB) system^{91 92} plays a key role in helping regulate physiological stress responses. It has also been linked to post-traumatic stress disorder (PTSD) and other stress-related psychological responses.⁹³ Although few studies have addressed the role of ECB genes in stress response, there is limited evidence suggesting a role for the fatty acid amide hydrolase (*FAAH*) and cannabinoid receptor-1 (*CNR1*) SNPs in PTSD.^{94 95} In addition, we have preliminary evidence that an *FAAH* gene SNP (rs324420) may be linked with acute stress response through interactions with the renin-angiotensin-aldosterone system (RAAS) and HPA axis SNPs (Holman *et al*, 2016 unpublished data).

Renin-angiotensin-aldosterone system

RAAS is a centerpiece of cardiovascular function and also contributes to both acute and chronic stress response, in part through its regulation of the sympathetic nervous system.⁸⁴ ACE inhibitors, a key component of RAAS, are essential for production of angiotensin II (AngII), a hormone with receptors throughout the HPA axis known to help regulate stress response in animals.⁸⁴ Reduced AngII is associated with fewer behavioral signs of anxiety and depression in animal models.^{84 96} RAAS-targeting drugs (angiotensin receptor blockers) help to alleviate stress's impact on health, especially neuropsychiatric and neurodegenerative diseases including stroke.⁸⁴ Although a handful of studies indicate that homozygotic T-allele carriers of the ACE promoter-region SNP rs4291 have higher plasma ACE activity (thus increasing AngII production) and hyperactive HPA axis responses,⁹⁷ very little is known about RAAS gene SNPs and stress response, particularly in the setting of stroke recovery.

Serotonergic system

The serotonergic system, discussed above in relation to drug pharmacogenetics, emerges again as a key factor in stroke recovery, here as a component to understanding stress. The 5-HTTLPR variable number of tandem repeats polymorphism is important to the serotonin stress response system, and has been extensively studied as a marker of genetic susceptibility to stress.⁹⁸ The presence of the low-expressing short allele has been identified as a 'sensitivity' marker for stress-related psychological effects. However, the impact of the 5-HTTLPR genotype on stress response is dependent in part on environmental experiences, especially the quality of one's social environment.⁹⁹ Consistent with this, imaging genetics studies further indicate that the 5-HTTLPR risk genotype is associated with amygdala activation following stress, making it an important candidate for this study.

GENETICS AS PART OF REHABILITATION THERAPY

Predicting behavioral recovery for an individual patient receiving rehabilitation therapy after stroke remains

challenging and imprecise.¹⁰⁰ The measures currently used to guide treatment planning for stroke rehabilitation are generally simple clinical assessments,^{101–103} which although useful fail to explain a substantial fraction of inter-subject variance in response to post-stroke rehabilitation therapy.^{104–106} Genetic factors related to physiological and psychological stress responses may prove useful in optimizing prescription of post-stroke rehabilitation therapy by elucidating which forms of rehabilitation are most effective for individual subjects.

CONCLUSIONS

Stroke remains a major source of human disability. New therapies can reduce initial injury but only a small fraction of patients reach medical systems in time to be eligible, and many of those so treated retain long-term disability. Therapies focused on neural repair may be able to improve outcomes for a large fraction of patients with stroke. In the prescription of rehabilitation therapies after stroke, high intersubject variability remains a major challenge. The current review considered a number of sources of genetic variation that might provide an improved understanding of differences in spontaneous recovery, and in response to a restorative therapy. Some genetic factors, such as polymorphisms in BDNF or dopamine-related proteins, are directly related to neural repair processes, while other factors, such as those related to the HPA axis or to RAAS, might impact recovery via psychological and physiological stress responses.

These efforts must be conducted with the strictest ethical standards given the highly sensitive nature of these data. A number of potential ethical concerns exist including, but not limited to, ensuring confidentiality of these sensitive data, adhering to the highest standards when obtaining informed consent from a patient who may not be fully competent, and maintaining a robust understanding of the uncertainty of genetic associations.⁸² A better understanding of these genetic factors stands to improve the precision with which clinical trials probe specific questions, as well as the ability to accurately individualize stroke patient care.

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