

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

Vanessa Juth,<sup>1</sup> E Alison Holman,<sup>1</sup> Michelle K Chan,<sup>1</sup> Steven C Cramer<sup>2</sup>

<sup>1</sup>Program in Nursing Science, UC Irvine, Irvine, California, USA

<sup>2</sup>Department of Neurology, UC Irvine, Orange, California, USA

## Correspondence to

Dr Steven C Cramer, Departments of Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation, University of California, Irvine, 200 S. Manchester Ave, Suite 206, Orange, CA 92868-4280 USA; [scramer@uci.edu](mailto:scramer@uci.edu)

Accepted 16 March 2016  
Published Online First  
4 April 2016

Copyright © 2016 American Federation for Medical Research

## 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.<sup>1</sup> As a result, there are >7,000,000 adult stroke survivors in the USA,<sup>2</sup> making stroke perennially among the leading causes of human disability<sup>3</sup> and the leading neurological cause of lost disability-adjusted life years.<sup>4</sup> Indeed, according to a recent American Heart Association Scientific Statement,<sup>5</sup> 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.<sup>6,7</sup>

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.<sup>8–11</sup> Motor deficits persist in 55–75% of patients and are associated with reduced quality of life.<sup>8–11</sup> 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.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup> 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



CrossMark

**To cite:** Juth V, Holman EA, Chan MK, et al. *J Investig Med* 2016;**64**:983–988.

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,<sup>16</sup> and may enhance recovery,<sup>17–21</sup> 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.<sup>22</sup> These include the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram,<sup>20 21 23–25</sup> the norepinephrine reuptake inhibitor reboxetine,<sup>26</sup> dopamine agonists such as L-dopa,<sup>17–19</sup> amphetamine,<sup>27–30</sup> methylphenidate,<sup>31 32</sup> and acetylcholinesterase inhibitors such as donepezil.<sup>33 34</sup> These drugs are prescribed at each physician's discretion.<sup>16</sup> 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 common<sup>39</sup> 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.<sup>40 41</sup> This BDNF val<sup>66</sup>met polymorphism has been associated with reduced short-term cortical plasticity in humans by several techniques,<sup>42–44</sup> with some evidence suggesting that this effect may be overcome with intense training.<sup>45</sup> Given the importance of cortical reorganization in the motor system after stroke, these studies suggest that the BDNF val<sup>66</sup>met 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 hemorrhage<sup>46</sup> and with poorer recovery and greater disability post-stroke,<sup>47</sup> although as in healthy subjects this effect might wane over time post-stroke.<sup>47</sup> This finding raises the question as to whether the 30–50% of human beings<sup>39</sup> 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,<sup>48 49</sup> and has been found to substantially affect the risk for Alzheimer's disease.<sup>50 51</sup> The presence of the ApoE epsilon4 polymorphism has been associated with poorer recovery and greater disability post-stroke<sup>47</sup> as well as poorer long-term outcome following several other conditions such as traumatic brain injury (TBI).<sup>52 53</sup> 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.<sup>54</sup> The COX-2 rs5275C and rs20417C alleles were associated with better outcome 90 days post-stroke.<sup>55</sup> 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.<sup>56</sup> In some cases, the function of the gene under study suggests specific therapeutic applications.<sup>57–59</sup> 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,<sup>17–19 60</sup> 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,<sup>61</sup> 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.<sup>61</sup> Similar results have been found using this gene score to study major depression<sup>62</sup> and impulse control.<sup>63</sup> 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,<sup>16</sup> but some studies suggest that such drugs may favorably influence other rehabilitation outcomes as well such as motor and cognitive measures.<sup>20 21 26</sup> 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,<sup>64</sup> although this effect is debated.<sup>65 66</sup> 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,<sup>67</sup> 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,<sup>64 68</sup> better response to psychosocial therapy<sup>69</sup> 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.<sup>70</sup> Meta-analysis has also found that SNPs in the genes for BDNF and tryptophan hydroxylase 1 may be associated with differences in antidepressant response.<sup>64</sup>

### 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.<sup>33 34</sup> Polymorphisms in the CYP2D6 gene (rs1065852 and rs1080985) have been associated with donepezil efficacy in AD,<sup>59 71–73</sup> and one such study also found higher blood plasma concentrations of donepezil with increasing CYP2D6\*10 alleles.<sup>71</sup> 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 tPA<sup>74</sup> and clopidogrel,<sup>75</sup> and in diverse conditions such as epilepsy,<sup>76</sup> diabetes,<sup>77</sup> rheumatoid arthritis,<sup>78</sup> cancer,<sup>79</sup> major depression,<sup>80</sup> and Parkinson's disease.<sup>81</sup> 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.<sup>82</sup>

## 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,<sup>83</sup> and can negatively impact the body's natural physiological functioning.<sup>84</sup> These stress-induced psychological and physiological responses are important because they may interfere with neural recovery,<sup>84 85</sup> 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.<sup>86 87</sup> 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.<sup>88</sup> This work generally characterizes the HPA axis response to *acute* stress as beneficial in that it mobilizes bodily resources to cope,<sup>88</sup> 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.<sup>89</sup> HPA axis SNPs also appear to be good candidates for testing gene-environment interactions in relation to indices of well-being.<sup>87–90</sup>

### Endocannabinoid system

The endocannabinoid (ECB) system<sup>91–92</sup> 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.<sup>93</sup> 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.<sup>94–95</sup> 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.<sup>84</sup> 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.<sup>84</sup> Reduced AngII is associated with fewer behavioral signs of anxiety and depression in animal models.<sup>84–96</sup> RAAS-targeting drugs (angiotensin receptor blockers) help to alleviate stress's impact on health, especially neuropsychiatric and neurodegenerative diseases including stroke.<sup>84</sup> Although a handful of studies indicate that homozygous T-allele carriers of the ACE promoter-region SNP rs4291 have higher plasma ACE activity (thus increasing AngII production) and hyperactive HPA axis responses,<sup>97</sup> 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.<sup>98</sup> 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.<sup>99</sup> 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.<sup>100</sup> The measures currently used to guide treatment planning for stroke rehabilitation are generally simple clinical assessments,<sup>101–103</sup> which although useful fail to explain a substantial fraction of inter-subject variance in response to post-stroke rehabilitation therapy.<sup>104–106</sup> 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.<sup>82</sup> 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.

**Contributors** All four authors (VJ, EAH, MKC, and SCC) contributed to the design, composition, and editing of this manuscript. All have made a significant contribution.

**Funding** SCC has served as a consultant to Roche, RAND Corporation, MicroTransponder, and Dart Neuroscience. This work was supported by K24 HD074722 and R01 NR015591.

**Competing interests** None declared.

**Provenance and peer review** Commissioned; externally peer reviewed.

### REFERENCES

- Lloyd-Jones D, Adams RJ, Brown TM, *et al*. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010;121:948–54.
- Roger VL, Go AS, Lloyd-Jones DM, *et al*. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2–220.
- Feigin VL, Lawes CM, Bennett DA, *et al*. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;2:43–53.
- Johnston SC, Hauser SL. Neurological disease on the global agenda. *Ann Neurol* 2008;64:A11–12.
- Miller EL, Murray L, Richards L, *et al*. American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient:



- a scientific statement from the American Heart Association. *Stroke* 2010;41:2402–48.
- 6 Reistetter TA, Karmarkar AM, Graham JE, et al. Regional variation in stroke rehabilitation outcomes. *Arch Phys Med Rehabil* 2014;95:29–38.
  - 7 MedPAC. *Report to the Congress: Medicare payment policy*. Washington DC: Medicare Payment Advisory Commission, 2012.
  - 8 Rathore S, Hinn A, Cooper L, et al. Characterization of incident stroke signs and symptoms: findings from the atherosclerosis risk in communities study. *Stroke* 2002;33:2718–21.
  - 9 Gresham G, Duncan P, Stason W, et al. *Post-Stroke Rehabilitation*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research, 1995.
  - 10 Saposnik G, Levin M, Outcome Research Canada (SORCan) Working Group. Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. *Stroke* 2011;42:1380–6.
  - 11 Gresham GE, Duncan PW, Stason WB, et al. Post-stroke rehabilitation: assessment, referral and patient-management. *Am Fam Physician* 1995;52:461–70.
  - 12 Goldstein L, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 2001;32:280–99.
  - 13 Edwards JD, Koehoorn M, Boyd LA, et al. Is health-related quality of life improving after stroke? A comparison of health utilities indices among Canadians with stroke between 1996 and 2005. *Stroke* 2010;41:996–1000.
  - 14 Cramer SC, Koroshetz WJ, Finklestein SP. The case for modality-specific outcome measures in clinical trials of stroke recovery-promoting agents. *Stroke* 2007;38:1393–5.
  - 15 Cramer SC, Sur M, Dobkin BH, et al. Harnessing neuroplasticity for clinical applications. *Brain* 2011;134(Pt 6):1591–609.
  - 16 Engelter ST, Urscheler N, Baronti F, et al. Frequency and determinants of using pharmacological enhancement in the clinical practice of in-hospital stroke rehabilitation. *Eur Neurol* 2012;68:28–33.
  - 17 Scheidtmann K, Fries W, Müller F, et al. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *Lancet* 2001;358:787–90.
  - 18 Floel A, Hummel F, Breitenstein C, et al. Dopaminergic effects on encoding of a motor memory in chronic stroke. *Neurology* 2005;65:472–4.
  - 19 Rosser N, Heuschmann P, Wersching H, et al. Levodopa improves procedural motor learning in chronic stroke patients. *Arch Phys Med Rehabil* 2008;89:1633–41.
  - 20 Chollet F, Tardy J, Albuher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011;10:123–30.
  - 21 Jorge RE, Robinson RG, Arndt S, et al. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry* 2003;160:1823–9.
  - 22 Engelter ST. Safety in pharmacological enhancement of stroke rehabilitation. *Eur J Phys Rehabil Med* 2013;49:261–7.
  - 23 Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. *Stroke* 1996;27:1211–14.
  - 24 Pariante J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. *Ann Neurol* 2001;50:718–29.
  - 25 Zittel S, Weiller C, Liepert J. Citalopram improves dexterity in chronic stroke patients. *Neurorehabil Neural Repair* 2008;22:311–14.
  - 26 Zittel S, Weiller C, Liepert J. Reboxetine improves motor function in chronic stroke. A pilot study. *J Neurol* 2007;254:197–201.
  - 27 Walker-Batson D, Smith P, Curtis S, et al. Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. *Stroke* 1995;26:2254–9.
  - 28 Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science* 1982;217:855–7.
  - 29 Martinsson L, Hardemark H, Eksborg S. Amphetamines for improving recovery after stroke. *Cochrane Db Syst Rev* 2007;(1):CD002090.
  - 30 Schuster C, Maunz G, Lutz K, et al. Dexamphetamine improves upper extremity outcome during rehabilitation after stroke: a pilot randomized controlled trial. *Neurorehabil Neural Repair* 2011;25:749–55.
  - 31 Grade C, Redford B, Chrostowski J, et al. Methylphenidate in early poststroke recovery: a double-blind, placebo-controlled study. *Arch Phys Med Rehabil* 1998;79:1047–50.
  - 32 Delbari A, Salman-Roghani R, Lökk J. Effect of methylphenidate and/or levodopa combined with physiotherapy on mood and cognition after stroke: a randomized, double-blind, placebo-controlled trial. *Eur Neurol* 2011;66:7–13.
  - 33 Berthier ML, Green C, Higuera C, et al. A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology* 2006;67:1687–9.
  - 34 Whyte EM, Lenze EJ, Butters M, et al. An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. *Cerebrovasc Dis* 2008;26:317–21.
  - 35 Pearson-Fuhrhop KM, Kleim JA, Cramer SC. Brain plasticity and genetic factors. *Top Stroke Rehabil* 2009;16:282–99.
  - 36 Pearson-Fuhrhop KM, Burke E, Cramer SC. The influence of genetic factors on brain plasticity and recovery after neural injury. *Curr Opin Neurol* 2012;25:682–8.
  - 37 Markus HS. Stroke genetics: prospects for personalized medicine. *BMC Med* 2012;10:113.
  - 38 Simon RP, Meller R, Zhou A, et al. Can genes modify stroke outcome and by what mechanisms? *Stroke* 2012;43:286–91.
  - 39 Shimizu E, Hashimoto K, Iyo M. Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. *Am J Med Genet B Neuropsychiatr Genet* 2004;126:122–3.
  - 40 Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003;112:257–69.
  - 41 Chen ZY, Patel PD, Sant G, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci* 2004;24:4401–11.
  - 42 Kleim JA, Chan S, Pringle E, et al. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. *Nat Neurosci* 2006;9:735–7.
  - 43 Cheeran B, Talelli P, Mori F, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J Physiol* 2008;586(Pt 23):5717–25.
  - 44 McHughen SA, Rodriguez PF, Kleim JA, et al. BDNF val66met polymorphism influences motor system function in the human brain. *Cereb Cortex* 2010;20:1254–62.
  - 45 McHughen SA, Pearson-Fuhrhop K, Ngo VK, et al. Intense training overcomes effects of the Val66Met BDNF polymorphism on short-term plasticity. *Exp Brain Res* 2011;213:415–22.
  - 46 Siironen J, Juvela S, Kanarek K, et al. The Met allele of the BDNF Val66Met polymorphism predicts poor outcome among survivors of aneurysmal subarachnoid hemorrhage. *Stroke* 2007;38:2858–60.
  - 47 Cramer SC, Proccaccio V. Correlation between genetic polymorphisms and stroke recovery: analysis of the GAIN Americas and GAIN International Studies. *Eur J Neurol* 2012;19:718–24.
  - 48 Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000;1:507–37.
  - 49 Cedazo-Minguez A. Apolipoprotein E and Alzheimer's disease: molecular mechanisms and therapeutic opportunities. *J Cell Mol Med* 2007;11:1227–38.
  - 50 Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–3.
  - 51 Hyman BT, Gomez-Isla T, Rebeck GW, et al. Epidemiological, clinical, and neuropathological study of apolipoprotein E genotype in Alzheimer's disease. *Ann N Y Acad Sci* 1996;802:1–5.
  - 52 Ponsford J, McLaren A, Schonberger M, et al. The association between apolipoprotein E and traumatic brain injury severity and functional outcome in a rehabilitation sample. *J Neurotrauma* 2011;28:1683–92.
  - 53 Zhou W, Xu D, Peng X, et al. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *J Neurotrauma* 2008;25:279–90.
  - 54 Marousi S, Ellul J, Antonacopoulou A, et al. Functional polymorphisms of interleukin 4 and interleukin 10 May predict evolution and functional outcome of an ischaemic stroke. *Eur J Neurol* 2011;18:637–43.
  - 55 Maguire J, Thakkinian A, Levi C, et al. Impact of COX-2 rs5275 and rs20417 and GP11a rs5918 polymorphisms on 90-day ischemic stroke functional outcome: a novel finding. *J Stroke Cerebrovasc Dis* 2011;20:134–44.
  - 56 Weaver SM, Chau A, Portelli JN, et al. Genetic polymorphisms influence recovery from traumatic brain injury. *Neuroscientist* 2012;18:631–44.
  - 57 Floresco SB, Jentsch JD. Pharmacological enhancement of memory and executive functioning in laboratory animals. *Neuropsychopharmacology* 2011;36:227–50.
  - 58 Husain M, Mehta MA. Cognitive enhancement by drugs in health and disease. *Trends Cogn Sci (Regul Ed)* 2011;15:28–36.
  - 59 Albani D, Martinelli Boneschi F, Biella G, et al. Replication study to confirm the role of CYP2D6 polymorphism rs1080985 on donepezil efficacy in Alzheimer's disease patients. *J Alzheimers Dis* 2012;30:745–9.

- 60 Sonde L, Lökk J. Effects of amphetamine and/or L-dopa and physiotherapy after stroke—a blinded randomized study. *Acta Neurol Scand* 2007;115:55–9.
- 61 Pearson-Fuhrhop KM, Minton B, Acevedo D, et al. Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-dopa. *PLoS ONE* 2013;8:e61197.
- 62 Pearson-Fuhrhop KM, Dunn EC, Mortero S, et al. Dopamine genetic risk score predicts depressive symptoms in healthy adults and adults with depression. *PLoS ONE* 2014;9:e93772.
- 63 MacDonald HJ, Stinear CM, Ren A, et al. Dopamine gene profiling to predict impulse control and effects of dopamine agonist ropinirole. *J Cogn Neurosci* 2016. In press.
- 64 Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatr* 2010;15:473–500.
- 65 Lewis G, Mulligan J, Wiles N, et al. Polymorphism of the 5-HT transporter and response to antidepressants: randomised controlled trial. *Br J Psychiatry* 2011;198:464–71.
- 66 McGuffin P, Alshabban S, Uher R. The truth about genetic variation in the serotonin transporter gene and response to stress and medication. *Br J Psychiatry* 2011;198:424–7.
- 67 Hadidi N, Treat-Jacobson DJ, Lindquist R. Poststroke depression and functional outcome: a critical review of literature. *Heart Lung* 2009;38:151–62.
- 68 Smits KM, Smits LJ, Schouten JS, et al. Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review. *Mol Psychiatr* 2004;9:433–41.
- 69 Kohen R, Cain KC, Buzaitis A, et al. Response to psychosocial treatment in poststroke depression is associated with serotonin transporter polymorphisms. *Stroke* 2011;42:2068–70.
- 70 Pinto N, Dolan ME. Clinically relevant genetic variations in drug metabolizing enzymes. *Curr Drug Metab* 2011;12:487–97.
- 71 Zhong Y, Zheng X, Miao Y, et al. Effect of CYP2D6\*10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. *Am J Med Sci* 2013;345:222–6.
- 72 Pilotto A, Franceschi M, D'Onofrio G, et al. Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease. *Neurology* 2009;73:761–7.
- 73 Seripa D, Bizzarro A, Pilotto A, et al. Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer's disease. *Pharmacogenet Genomics* 2011;21:225–30.
- 74 Samson RD, Frank MJ, Fellous JM. Computational models of reinforcement learning: the role of dopamine as a reward signal. *Cogn Neurodyn* 2010;4:91–105.
- 75 Mega JL, Hochholzer W, Frelinger AL III, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA* 2011;306:2221–8.
- 76 Depondt C, Godard P, Espel RS, et al. A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. *Eur J Neurol* 2011;18:1159–64.
- 77 Tarasova L, Kalnina I, Geldner K, et al. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion 1 transporter protein genes with the gastrointestinal side effects and lower BMI in metformin-treated type 2 diabetes patients. *Pharmacogenet Genomics* 2012;22:659–66.
- 78 Jekic B, Lukovic L, Bunjevacki V, et al. Association of the TYMS 3G/3G genotype with poor response and GGH 354GG genotype with the bone marrow toxicity of the methotrexate in RA patients. *Eur J Clin Pharmacol* 2013;69:377–83.
- 79 Leandro-Garcia LJ, Leskela S, Jara C, et al. Regulatory polymorphisms in  $\beta$ -tubulin IIa are associated with paclitaxel-induced peripheral neuropathy. *Clin Cancer Res* 2012;18:4441–8.
- 80 Kawashima S, Ueki Y, Kato T, et al. Changes in striatal dopamine release associated with human motor-skill acquisition. *PLoS ONE* 2012;7:e31728.
- 81 Kalinderi K, Fidani L, Katsarou Z, et al. Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease. *Int J Clin Pract* 2011;65:1289–94.
- 82 Shamy MC, Zai C, Basile VS, et al. Ethical and policy considerations in the application of pharmacogenomic testing for tardive dyskinesia: case study of the dopamine D3 receptor. *Curr Pharmacogenomics Person Med* 2011;9:94–101.
- 83 Ayerbe L, Ayis S, Crichton S, et al. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. *J Neurol Neurosurg Psychiatr* 2014;85:514–21.
- 84 Saavedra JM, Sanchez-Lemus E, Benicky J. Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: therapeutic implications. *Psychoneuroendocrinology* 2011;36:1–18.
- 85 McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron* 2013;79:16–29.
- 86 Holman EA, Lucas-Thompson RG, Lu T. Social constraints, genetic vulnerability, and mental health following collective stress. *J Trauma Stress* 2011;24:497–505.
- 87 Lessard J, Holman EA. FKBP5 and CRHR1 polymorphisms moderate the stress-physical health association in a national sample. *Health Psychol* 2014;33:1046–56.
- 88 McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338:171–9.
- 89 Bogdan R, Hyde LW, Hariri AR. A neurogenetics approach to understanding individual differences in brain, behavior, and risk for psychopathology. *Mol Psychiatry* 2013;18:288–99.
- 90 Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA* 2008;299:1291–305.
- 91 Hill MN, McLaughlin RJ, Bingham B, et al. Endogenous cannabinoid signaling is essential for stress adaptation. *Proc Natl Acad Sci USA* 2010;107:9406–11.
- 92 Hill MN, Tasker JG. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. *Neuroscience* 2012;204:5–16.
- 93 Neumeister A, Normandin MD, Pietrzak RH, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. *Mol Psychiatry* 2013;18:1034–40.
- 94 Gunduz-Cinar O, MacPherson KP, Cinar R, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. *Mol Psychiatry* 2013;18:813–23.
- 95 Pitman RK, Rasmusson AM, Koenen KC, et al. Biological studies of post-traumatic stress disorder. *Nat Rev Neurosci* 2012;13:769–87.
- 96 Aguilera G, Kiss A, Luo X, et al. The renin angiotensin system and the stress response. *Ann N Y Acad Sci* 1995;771:173–86.
- 97 Baghai TC, Binder EB, Schule C, et al. Polymorphisms in the angiotensin-converting enzyme gene are associated with unipolar depression, ACE activity and hypercortisolism. *Mol Psychiatry* 2006;11:1003–15.
- 98 Caspi A, Hariri AR, Holmes A, et al. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry* 2010;167:509–27.
- 99 Taylor SE, Way BM, Welch WT, et al. Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biol Psychiatry* 2006;60:671–6.
- 100 Stinear C. Prediction of recovery of motor function after stroke. *Lancet Neurol* 2010;9:1228–32.
- 101 Hakkennes SJ, Brock K, Hill KD. Selection for inpatient rehabilitation after acute stroke: a systematic review of the literature. *Arch Phys Med Rehab* 2011;92:2057–70.
- 102 Hakkennes S, Hill KD, Brock K, et al. Selection for inpatient rehabilitation after severe stroke: what factors influence rehabilitation assessor decision-making? *J Rehabil Med* 2013;45:24–31.
- 103 Hakkennes S, Hill KD, Brock K, et al. Accessing inpatient rehabilitation after acute severe stroke: age, mobility, prestroke function and hospital unit are associated with discharge to inpatient rehabilitation. *Int J Rehabil Res* 2012;35:323–9.
- 104 Chang EY, Chang EH, Cragg S, et al. Predictors of gains during inpatient rehabilitation in patients with stroke: a review. *Crit Rev Phys Rehabil Med* 2013;25:203–221.
- 105 Ng Y, Astrid S, De Silva D, et al. Functional outcomes after inpatient rehabilitation in a prospective stroke cohort. *Proc Singapore Health* 2013;22:175–82.
- 106 Burke Quinlan E, Dodakian L, See J, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. *Ann Neurol* 2015;77:132–45.