Int J Physiol Pathophysiol Pharmacol 2019;11(1):1-11
www.ijppp.org /ISSN:1944-8171/IJPPP0086608

Review Article

Post-stroke neuronal circuits and mental illnesses

Farzaneh Sadat Naghavi, Erin E Koffman, Boren Lin, Jianyang Du

Department of Biological Sciences, The University of Toledo, Toledo, Ohio

Received October 11, 2018; Accepted January 13, 2019; Epub February 15, 2019; Published February 28, 2019

Abstract: Stroke is one of the leading causes of death in the United States. It is also associated with severe mental illnesses, such as depression and anxiety, that hinder the rehabilitation of surviving patients. Thus, a better understanding of how stroke causes mental illnesses is crucial, but little is known about the neurological mechanisms involved. In this review, we summarized the most common mental illnesses developed after stroke, as well as the underlying mechanisms at the neuronal circuit level.

Keywords: Stroke, post-stroke mental disorders, post-stroke neuronal circuits

Introduction

Stroke is defined as any central nervous system (CNS) damage resulting from an abnormal blood supply [1] and is one of the leading causes of death in the United States. Stroke classifications include cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis, and spinal cord stroke. Cerebral infarction itself is subdivided into four categories: lacunar, atherothrombotic, cardioembolic, and undetermined types [2]. The incidence of stroke and the frequency of stroke subtypes can be influenced by several factors, including age, race, and sex [3, 4].

According to the recent stroke statistics report from the U.S. Centers for Disease Control and Prevention, over 795,000 Americans are affected by stroke annually, with about 140,000 dying, while survivors are at risk for serious long-term disability [5]. Many stroke survivors suffer physical, cognitive or mental impairment and need continuous support for daily activities. In most cases, this has a direct psychological, social, and economic impact on both the patients and their families. Thus, there is a growing need for research and development to improve prevention of and recovery from stroke and its complications. This review summarizes the mental disorders that are associated with stroke and highlights the mechanisms underlying its pathophysiology in the brain remapping that occurs during recovery.

Changes in neural circuits after stroke

Ischemic damage can affect various components of brain structures-most notably neurons, astrocytes, pericytes, the cerebral microvascular endothelium, and the extracellular matrix of the basal lamina [6, 7]. The core region of stroke is not the only part of the brain that undergoes apoptosis and necrosis following stroke. It is often bordered by a region called penumbra, a portion of the ischemic territory that is still potentially salvageable. A penumbra may undergo a process called reperfusion if blood flow is restored with partial recovery of structure, which allows for survival and contribution to synaptic networks. However, neurons can only survive for a limited time and will die if reperfusion does not occur within sevel hours or days [8, 9]. In neurons, the deprivation of oxygen and energy during a stroke can lead to signs of structural damage within two minutes of stroke [8]. Multiple short and long-term changes in brain after stroke may result in an imbalance of excitatory and inhibitory neuronal circuits [10]. It is well known that changing in both γ-aminobutyric acid (GABA) and glutamate neurotransmissions, as principle inhibitory and primary excitatory neurotransmitters alter neuronal activities [11]. In cortical areas adjacent

to infarcts, long-term potentiation (LTP) induction was thought to be due to a down regulation of GABA receptor activity [12]. Electrophysiological and receptor autoradiography data shows that stroke events can cause a long-lasting decrease in $GABA_A$ receptor $GABA_A$ R binding sites and an increase in NMDA receptor binding sites in the cortex [13, 14]. These changes take place both adjacent and contralateral to the infarct, diminishing inhibitory post-synaptic potentials and boosting excitatory post-synaptic potentials [13, 14]. Models of recovery from stroke are associated with enhanced glutamate signaling through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and downstream induction of brain-derived neurotrophic factor (BDNF); the latter will, in turn, lead to changes in axonal structure [12, 15].

Within weeks of a stroke event, inhibition through phasic GABA signaling is reduced and focal brain damage leads to a decreased density of inhibitory interneurons [16, 17]. Treatment with $GABA_A$ R agonists at the time of stroke leads to decreased stroke size [18]. However, Clarkson and colleagues indicated that the timing of drug administration is important in treating patients for stroke; tonic inhibition soon after stroke led to an increase in cell death and exacerbated stroke damage, whereas a three-day delay in treatment led to improved functional recovery without altering the size of the area affected by the stroke [19]. In spite of the fact that inhibition of tonic GABA signaling during the repair phase had a beneficial effect on the recovery of neuronal function in mice, an increase in phasic GABA signaling using zolpidem during the repair phase enhanced behavioral recovery [20]. A clear understanding of the interplay between phasic and tonic GABA signaling in modulating stroke recovery requires further investigation.

After stroke, spontaneous recovery occurs through brain remapping. Newly developed brain circuits lead to different behavioral patterns and new response strategies to recover performance [9]. Several animal studies have shown that increases in gene expression are essential for the growth of neurons, synaptogenesis, and growth of dendritic spines following stroke [21-24]. These studies also show that neuroplastic processes observed during increased gene expression are similar to those that occur during development [21-24]. However, the correlation between such intrinsic compensatory structural rearrangement in the mammalian central nervous system (CNS) (spontaneous recovery) and the recovery of the brain function (performance recovery) has not yet been demonstrated [25]. Spontaneous recovery circuit remapping is associated with dramatic plasticity of dendritic spines within the region surrounding the infarct, and with an increase in spine density in some regions [26]. Rewiring of neuronal connections can lead to the activation of several plasticity mechanisms, such as the release of activity-dependent neurotrophins. These neurotrophins, specifically brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) have been shown to improve recovery by increasing axonal and dendritic sprouting [27-30]. In 2014, Cheng and colleagues used an optogenetic approach to demonstrate that selectively stimulating neurons in layer V of the cortex increased the expression of activity-dependent neurotrophins, such as BDNF and NGF, in the contralesional cortex. Notably, stimulation of neurons in the ipsilesional primary motor-cortex (iM1) improved the recovery of function [31]. Cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), a transcription factor for BDNF, also plays a role in recovery after stroke. Caracciolo and colleagues found that virus-mediated over-expression of CREB in the anterior regions of peri-infarct motor neurons enhanced recovery and increased neuronal excitability and plasticity. Interestingly, these effects were reversible, suggesting that motor recovery can be switched off or on, respectively, by blocking or inducing CREB signaling [32].

The process of motor recovery after stroke has also been associated with the recruitment of neighboring areas of the motor and somatosensory cortices [13, 14]. In 2009, Takatsuru and colleagues reported that the left somatosensory cortex compensates for loss of function in the right somatosensory cortex by establishing new neuronal circuits and/or remapping the neuronal circuits [33]. In addition, Starkey and colleagues suggested that motor circuits are substantially remapped after focal ischemia, and that the extent of recovery likely correlates with sprouting of neurons from hind limb sensory-motor cortex into the cervical spinal cord

sprouting of new connections [34]. A study published in 2010 by van Meer and colleagues found that within a few days of stroke, a significant loss of functional connectivity between the two brain hemispheres was compensated by interhemispheric coupling accompanied by behavioral improvement [35].

Post-stroke mental illnesses

The neuroplasticity observed in the brain after a stroke can either accelerate recovery or lead to unexpected behavioral changes that result in mental illnesses [36]. Such psychiatric disorders in a patient can negatively affect quality of life and lead to further complications including increased risk of stroke recurrence, suicidal tendencies, or interference with stroke recovery [37]. Mental illnesses that are commonly associated with stroke are depression [38], anxiety [39], fatigue [40], sleep disturbances [41], and emotionalism [42].

Depression

Depression has only recently been studied as a significant long-term problem in patients with brain injury, and as a result, post-stroke depression is often under-diagnosed and under-treated. Among stroke survivors, 33% show symptoms of depression, and 40% of patients with depression remain symptomatic for at least one year post-stroke event [44, 45]. The major contributing factor to PSD is thought to be mental distress caused by post-stroke physical disabilities [45, 46]. Studies comparing the incidence of depression in stroke patients to patients with disabilities not caused by stroke have suggested that post-stroke cerebral lesions may be a significant contributing factor to PSD [45, 46]. The dorsolateral prefrontal cortex (DLPFC) is an important node of the cognitive control network (CCN), a neuronal circuit that contributes to the modulation of attention and working memory [47]. Lesions in both the right and left DLPFC are associated with depression, but a recent study showed that the severity of stroke outcomes correlates with the extent of damage to the left side [48]. Egorova and colleagues showed that stroke patients can experience depression, even in the absence of a lesion in the left DLPFC, due to low connectivity between this region and the supramarginal gyrus (SMG) [49]. The SMG is located at the border of the parietal and temporal cortices and is connected to the angular gyrus; together these two structures form the temporoparietal junction. This junction is engaged in memory, social processing, and attention [50] and together with the DLPFC, is termed the 'rich-club' [51]. PSD can be associated with the presence of a lesion on either side of the brain, although lesions typically occur in the left hemisphere [52, 53]. Several studies have suggested that lesions in the cortico-limbic circuitry and alterations in neural activity and projections between the PFC and the basal ganglia could contribute to depression after stroke [54-56].

The neurobiological mechanisms underlying PSD could potentially be revealed by studying the regulatory molecules of this disease. Currently we know that anti-depressents classified as selective serotonin reuptake inhibitors (SSRIs) have a beneficial effect on the post-ischemic outcome. Stroke patients with a polymorphism in the promoter of the gene encoding the serotonin transporter protein (5-HTTLPR) are at higher risk for developing PSD than others [45, 57]. Increases in the expression levels of pro-inflammatory cytokines, such as interleukin 1 beta (IL-1β), IL-6 and tumor-necrosis factor alpha (TNFα) lead to increased leukocyte infiltration and are associated with a reduction of serotonin (5HT) in some brain regions, including the basal ganglia, paralimbic regions, and ventral/lateral frontal cortex [58]. Such increases may result in the onset of depression and breathing disturbances during sleep [59]. Stroke is also associated with inflammation due to tissue damage and induction of the expression and activation of cytokines such as TNFs, ILs, and interferons (IFNs). These molecules affect neural plasticity, neurotransmitter metabolism, and neuroendocrine function and are contribute to PSD [60]. Although stroke is also associated with enhanced glucocorticoid (GC) secretion [61], the relationship between stroke, GC secretion, cytokine activity, and mental illnesses are not well defined.

An adipocyte hormone, leptin, is considered a vascular risk factor for myocardial infarct and stroke [62]. Although its role in the development of depression remains controversial and unclear, some studies have shown an association between high leptin levels and PSD [43, 63, 64]. Leptin and GC are known to have a

reciprocal relationship, acting in a positive feedback loop. In adipose tissue, leptin can activate the HPA axis, leading to GC induction; this in turn causes an increase in the synthesis and secretion of leptin [43]. Leptin activated by inflammatory cytokines also plays a role in immune responses [65]. The well-studied neurotropin BDNF might be another candidate molecule that could explain the complicated relationship between depression, antidepressant and post-stroke recovery, although limited research has specifically studied the role of BDNF in PSD. It has been shown that in stroke survivors with PSD the concentration of serum BDNF decreased within 3-6 months of a stroke event [66]. Moreover, a BDNF Val66Met polymorphism has been suggested to be responsible for the association between stroke and depression [67]. BDNF is likely involved in PSD and other mental illnesses after stroke because it acts as an antidepressant [68] and reduces apoptosis *in vitro* after glucose deprivation [68].

PSD is related to a range of adverse health consequences such as increased disability and mortality [69], and its symptoms may become worse during the chronic phase [45]. Stroke patients with depression are at high risk for suicide and increased mortality [70-72]. In another systematic review, Wu and colleagues showed that post-stroke fatigue is directly associated with depressive symptoms and directly or indirectly associated with anxiety, poor coping, loss of control, emotional disorders, and behavioral disorders [73].

Anxiety

After a stroke event, patients are at increased risk of developing anxiety. About 25-50% of patients show anxiety during the acute phase of stroke, and young patients and those with a history of anxiety or depression are more likely to develop anxiety after stroke [74, 75]. Longitudinal data suggests that post-stroke anxiety (PSA) can last as long as ten years [76]. The following symptoms of anxiety have been reported in patients after stroke: physiological arousal (increased heart rate); avoidance of stress; cognitive disruption; hypersensitivity to possible threatening cues and waiting for adverse events to occur unpredictably; avoidance of crowded places, sexual intercourse, being home alone, going out alone, and traveling on public transport; activities related to fear of having another stroke; and headache [74, 77]. In 2018, *Chun et al.* found that a major contributing factor to anxiety in post-stroke patients is fear of stroke recurrence [74].

At the molecular level several studies have shown that following cerebral ischemia, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is activated in neurons [78, 79], endothelial cells, astrocytes, and microglia [80, 81]. However, whether the role of NF-kB is protective or pathogenic remains unclear. One study that supports a detrimental role in cerebral ischemia revealed that in transgenic mice lacking the NF-kB subunit p50, infarct size decreased significantly; this was the case for models of both transient and permanent stroke [79]. However, in other studies NF-kB protected against neuronal death [82]. In addition, another study suggested that the activation of NF-kB in glia may worsen ischemia through NF-kB-dependent activation of microglia, whereas activation in neurons might be important for other processes like memory [83]. A recent study by *Zhu et al.* showed that hippocampal NF-kB mediates anxiogenic behaviors, likely through enhancing the expression and association of nNOS-CAPON-Dexras [84]. *Yeh et al*. 2002, showed that activation of NF-B in the amygdala was required for fear conditioning [85], and that in the context of a lack of the NF-kB subunit p50, anxiety-like and fear-like responses were less extreme [86]. Few studies have shed light on the mechanisms underlying post-stroke anxiety, and further research exploring the role of brain networks involved in these mental illnesses is needed.

Fatigue

Fatigue is a common symptom in patients with neurological diseases developed via various biological mechanisms. Examples include systemic lupus erythematous [87], multiple sclerosis [88], Parkinson's disease [89] and stroke [90]. Post-stroke fatigue has been found to occur in 40-74% of stroke patients [90], yet the pathophysiology remains poorly understood [91]. Fatigue is sometimes evaluated subjectively, based on a patient's feeling of weariness, early tiredness or unwillingness to exert effort; in other studies it is evaluated objective-

ly, based on a measurable reduction in performance during the repetition of a physical or mental task [92]. Several factors may contribute to post-stroke fatigue, including physical impairment, disuse, sleep disorders, and depression [93, 94]. High post-stroke fatigue is associated with low motor cortical excitability in the lesioned hemisphere, suggesting that post-stroke fatigue may be a direct consequence of changes in corticomotor control on the affected side [95, 96], although such a correlation remains to be documented. Stroke survivors experience more mental and physical fatigue than the general population, which allows fatigue to be considered a multidimensional phenomenon [97].

Some studies have suggested that pituitary dysfunction (PD) is comorbid with stroke and that the PD contributes to the development of post-stroke fatigue [98]. Recent studies have demonstrated that serum levels of glucose and uric acid (UA) are closely associated with stroke [99, 100]. UA is a product of purine metabolism and a neuroprotective antioxidant [101]. Both a low level of serum UA and a high level of serum glucose are associated with increased fatigue severity scale (FSS) scores during the acute stage of stroke [102]. Therefore, a stroke patient may develop fatigue and then disability, which may prevent reestablishment of professional and social activities.

Sleep disorders

The sleep disorders characterized as sleep-disordered breathing (SDB) and sleep-wake disorders (SWDs) can be either risk factors for or symptoms of stroke [103]. Approximately 50%-70% and 10%-50% of stroke patients have SDB and SWD, respectively [41]. SDB refers to habitual snoring, obstructive sleep apnea (OSA), and central sleep apnea (CSA) [41].

SDB is more common in recurrent versus new stroke patients, and CSA is usually linked to injury of central autonomic networks such as those of the insular cortex and the thalamus [104, 105]. In a recent study it was observed that wakefulness disorders resulting as a consequence of SDB, including hypersomnia, excessive daytime sleepiness (EDS) and fatigue are common after stroke [106]. In spite of the fact that no link has been discovered between SDB and stroke severity, topography or presumed etiology [107-109], these symptoms have negative effects on rehabilitation and quality of life due to their association with depression, anxiety and cognitive disturbances [110]. Both habitual snoring and OSA are considered independent risk factors for stroke in elderly and middle-aged adults [111-112]. Habitual snoring is strongly associated with stroke and may be a risk factor for ischemic stroke [113]. Acute stroke, especially with involvement of the thalamo-mesencephalic structures, is frequently accompanied by an increase in daytime sleepiness [41]. Therefore, CSA may be a consequence, rather than a cause of stroke and can be a heralding symptom of the vascular disease.

Along with SDB, SWD are also frequently observed in stroke patients and can affect stroke outcomes, yet they have not been investigated in detail [41]. Insomnia, sleep-related movement disorders (e.g. restless legs syndrome, periodic limb movement during sleep), disturbances of wakefulness (e.g. hypersomnia, excessive daytime sleepiness, fatigue), and parasomnias (e.g. REM sleep behavior disorder) are SWDs and are found in 10%-50% of stroke patients [41]. In addition, insomnia was found to be related to brainstem damage and most commonly linked to post-stroke complications [62]. One study showed that 57% of stroke patients suffer insomnia in the first month after the onset of stroke [61]. A population study showed that patients suffering from insomnia have a high mortality rate [63], but the effect of insomnia on mortality after stroke remains unknown. A meta-analysis showed that both short sleep duration and long sleep duration are predictors of ischemic stroke [114]. Pharmacologic studies suggested that the cAMP/protein kinase A (PKA) pathway might be involved in the regulation of wakefulness and rapid eye movement (REM) sleep [115]. Another study showed that the cAMP/MAPK/CREB transcriptional pathway is activated during REM sleep, but not non-rapid eye movement (NREM) sleep [116]. The study also found this pathway may contribute to hippocampus-dependent memory consolidation [116]. Neither the effect of sleep disorders on the occurrence and recurrence of stroke, nor the neurological pathway associated with post-stroke sleep disorders has been fully elucidated. Further evalu-

ation of the treatment of post-stroke sleep disorders to improve stroke rehabilitation and stroke outcomes, including mood and cognitive function, would be beneficial. Findings from such studies are expected to lead to the discovery of novel targets in therapies for this stroke-associated mental illness.

Emotionalism

Emotionalism (emotional lability) refers to an increase in the frequency of crying or laughing in a social situation in response to non-emotive or incongruous stimuli. Emotionalism is another common psychological condition that can hinder stroke recovery. About 20-25% of stroke patients are afflicted with emotionalism during the first 6 months after stroke, and 10-15% of affected patients remain symptomatic after one year [42]. The rate of co-occurrence for depression and emotionalism is 38%, and emotionalism develops more often in patients with PSD than in those without depression [117]. Different terminology has been used in reporting characteristics of emotionalism, for example pathological laughing and crying (PLC), emotional incontinence, and emotional lability. However, in 1989 House and colleagues introduced 'emotionalism' as a general term for all such emotional disorders, to define the habit of weakly yielding to emotion [118]. This group found that persistent emotionalism is associated with anterior lesions in the left hemisphere, and this association has been reported after unilateral stroke. However, the correlation between lesion location and the emergence of emotionalism remains unclear. Some studies have reported that the basal ganglia, pons, cerebral cortex, and cerebellum are all involved in emotionalism [119-121]. Others have shown that chemical changes in the circuits that interconnect the frontal/temporal lobe, basal ganglia, and ventral brainstem may affect the development of emotionalism [119]. Parvizi and colleagues suggested that emotionalism is caused by dysfunction in circuits that involve the cerebellum and exert an impact on brainstem nuclei and the cerebral cortex itself [120]. Another study suggested that dysfunction of a serotonergic system due to partial destruction of the serotonergic raphe nuclei or projections from these nuclei to the hemispheres might underlie emotionalism [122]. It has been indicated that lesions in the lenticulocapsular region, basis pontis, medulla oblongata or cerebellum are more likely related to emotionalism [120]. Moreover, stroke survivors with paramedian basilar infarct showed pathological laughing [123].

Although the etiology of post-stroke emotionalism is unknown, several hypotheses have been proposed, including lesions and imbalances in serotonergic neurotransmission. Some studies have implicated dysfunction of serotonergic neurotransmission as a cause. Using single-photon emission computerized tomography, it has been shown that serotonin-based neurotransmission is reduced in patients suffering post-stroke emotionalism due to an abnormally low density of serotonintransporter (SERT) in the midbrain and pons [124]. Data from another study in which serotonergic neurotransmission was measured using positron emission tomography (PET) suggested that either neurotransmitter depletion or an increase in affinity of the receptor for the neurotransmitter could cause of an increase in binding potential [125]. The binding potential of the 5-HT1A receptor antagonist in limbic areas and raphe nuclei was high, whereas that in the basal ganglia and cerebellum was negligible, suggesting that serotonergic neurotransmission is abnormally low during the early phase of stroke [125].

Conclusion

Stroke is not only associated with high mortality, but is also a risk factor for multiple mental illnesses that significantly hinder rehabilitation of stroke survivors. Most recent studies have suggested that the mechanisms responsible for post-stroke illness might be centralized, affecting mainly the remodeled emotional neuronal circuits after a stroke. However, many questions remain unanswered, including how the post-stroke neuronal circuits are rewired, as well as to what extent and how the infarction area influences remote areas of damage, and thus how behavior is enhanced or inhibited. These unanswered questions open doors for research, advances, and improved treatment and outcomes for stroke survivors in the future.

Acknowledgements

This work was supported by the American Heart Association (15SDG25700054) and The

National Institute of Mental Health (1R01MH-113986-01A1).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jianyang Du, Department of Biological Sciences, The University of Toledo, Toledo, Ohio. Tel: (419) 530-2824; E-mail: jianyang.du@utoledo.edu

References

[1] Mackay J, Mensah GA, Greenlund K. The atlas of heart disease and stroke: World Health Organization; 2004.
[2] Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. Cerebrovasc Dis 2009; 27: 493-501.
[3] Gresham GE, Stason WB, Duncan PW. Post-stroke rehabilitation: diane publishing company; 1997.
[4] Arima H, Tanizaki Y, Yonemoto K, Doi Y, Ninomiya T, Hata J, Fukuhara M, Matsumura K, Iida M, Kiyohara Y. Impact of blood pressure levels on different types of stroke: the Hisayama study. J Hypertens 2009; 27: 2437-43.
[5] Preventing Stroke Deaths [Internet]. national center for chronic disease prevention and health promotion. 2017. Available from: https://www.cdc.gov/vitalsigns/pdf/2017-09-vitalsigns.pdf.
[6] Zhang L, Zhang ZG, Chopp M. The neurovascular unit and combination treatment strategies for stroke. Trends Pharmacol Sci 2012; 33: 415-22.
[7] Wong AD, Ye M, Levy AF, Rothstein JD, Bergles DE, Searson PC. The blood-brain barrier: an engineering perspective. Front Neuroeng 2013; 6: 7.
[8] Murphy TH, Li P, Betts K, Liu R. Two-photon imaging of stroke onset in vivo reveals that NMDA-receptor independent ischemic depolarization is the major cause of rapid reversible damage to dendrites and spines. J Neurosci 2008; 28: 1756-72.
[9] Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci 2009; 10: 861-72.
[10] Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. Curr Neurol Neurosci Rep 2015; 15: 27.
[11] Carmichael S. Brain excitability in stroke: the yin and yang of stroke progression. Arch Neurol 2012; 69: 161-7.
[12] Hagemann G, Redecker C, Neumann-Haefelin T, Freund HJ, Witte OW. Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. Ann Neurol 1998; 44: 255-8.
[13] Carmichael ST. Plasticity of cortical projections after stroke. Neuroscientist 2003; 9: 64-75.
[14] Butefisch CM. Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke. Neuroscientist 2004; 10: 163-73.
[15] Schäbitz WR, Steigleder T, Cooper-Kuhn CM, Schwab S, Sommer C, Schneider A, Kuhn HG. Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. Stroke 2007; 38: 2165-72.
[16] Alia C, Spalletti C, Lai S, Panarese A, Micera S, Caleo M. Reducing GABAA-mediated inhibition improves forelimb motor function after focal cortical stroke in mice. Sci Rep 2016; 6: 37823.
[17] Zeiler SR, Gibson EM, Hoesch RE, Li MY, Worley PF, O'Brien RJ, Krakauer JW. Medial premotor cortex shows a reduction in inhibitory markers and mediates recovery in a mouse model of focal stroke. Stroke 2013; 44: 483-9.
[18] Cui Y, Costa RM, Murphy GG, Elgersma Y, Zhu Y, Gutmann DH, Parada LF, Mody I, Silva AJ. Neurofibromin regulation of ERK signaling modulates GABA release and learning. Cell 2008; 135: 549-60.
[19] Clarkson AN, Huang BS, MacIsaac SE, Mody I, Carmichael ST. Reducing excessive GABAergic tonic inhibition promotes post-stroke functional recovery. Nature 2010; 468: 305-9.
[20] Hiu T, Farzampour Z, Paz JT, Wang EH, Badgely C, Olson A, Micheva KD, Wang G, Lemmens R, Tran KV, Nishiyama Y, Liang X, Hamilton SA, O'Rourke N, Smith SJ, Huguenard JR, Bliss TM, Steinberg GK. Enhanced phasic GABA inhibition during the repair phase of stroke: a novel therapeutic target. Brain 2016; 139: 468-80.
[21] Carmichael ST, Archibeque I, Luke L, Nolan T, Momiy J, Li S. Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. Exp Neurol 2005; 193: 291-311.
[22] Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res 2008; 51: S225-39.
[23] Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol 2006; 59: 735-42.
[24] Cramer SC, Chopp M. Recovery recapitulates ontogeny. Trends Neurosci 2000; 23: 265-71.
[25] Weidner N, Ner A, Salimi N, Tuszynski MH. Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. Proc Natl Acad Sci U S A 2001; 98: 3513-8.

[26] Rivera-Urbina GN, Batsikadze G, Molero-Chamizo A, Paulus W, Kuo MF, Nitsche MA. Parietal transcranial direct current stimulation modulates primary motor cortex excitability. Eur J Neurosci 2015; 41: 845-55.
[27] Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann N Y Acad Sci 2008; 1144: 97-112.
[28] Zhu W, Cheng S, Xu G, Ma M, Zhou Z, Liu D, Liu X. Intranasal nerve growth factor enhances striatal neurogenesis in adult rats with focal cerebral ischemia. Drug Deliv 2011; 18: 338-43.
[29] Markus A, Patel TD, Snider WD. Neurotrophic factors and axonal growth. Curr Opin Neurobiol 2002; 12: 523-31.
[30] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010; 66: 198-204.
[31] Cheng MY, Wang EH, Woodson WJ, Wang S, Sun G, Lee AG, Arac A, Fenno LE, Deisseroth K, Steinberg GK. Optogenetic neuronal stimulation promotes functional recovery after stroke. Proc Natl Acad Sci U S A 2014; 111: 12913-8.
[32] Caracciolo L, Marosi M, Mazzitelli J, Latifi S, Sano Y, Galvan L, Kawaguchi R, Holley S, Levine MS, Coppola G, Portera-Cailliau C, Silva AJ, Carmichael ST. CREB controls cortical circuit plasticity and functional recovery after stroke. Nat Commun 2018; 9: 2250.
[33] Takatsuru Y, Fukumoto D, Yoshitomo M, Nemoto T, Tsukada H, Nabekura J. Neuronal circuit remodeling in the contralateral cortical hemisphere during functional recovery from cerebral infarction. J Neurosci 2009; 29: 10081-6.
[34] Starkey ML, Bleul C, Zörner B, Lindau NT, Mueggler T, Rudin M, Schwab ME. Back seat driving: hindlimb corticospinal neurons assume forelimb control following ischaemic stroke. Brain 2012; 135: 3265-81.
[35] van Meer MP, van der Marel K, Wang K, Otte WM, El Bouazati S, Roeling TA, Viergever MA, Berkelbach van der Sprenkel JW, Dijkhuizen RM. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. J Neurosci 2010; 30: 3964-72.
[36] Huang CCY, Ma T, Roltsch Hellard EA, Wang X, Selvamani A, Lu J, Sohrabji F, Wang J. Stroke triggers nigrostriatal plasticity and increases alcohol consumption in rats. Sci Rep 2017; 7: 2501.
[37] Vahid-Ansari F, Lagace DC, Albert PR. Persistent post-stroke depression in mice following unilateral medial prefrontal cortical stroke. Transl Psychiatry 2016; 6: e863.
[38] De Wit L, Putman K, Baert I, Lincoln NB, Angst F, Beyens H, Bogaerts K, Brinkmann N, Connell L, Dejaeger E, De Weerdt W, Jenni W, Kaske C, Komarek A, Lesaffre E, Leys M, Louckx F, Schuback B, Schupp W, Smith B, Feys H. Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. Disabil Rehabil 2008; 30: 1858-66.
[39] Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. Disabil Rehabil 2013; 35: 291-9.
[40] Choi-Kwon S, Kim JS. Poststroke fatigue: an emerging, critical issue in stroke medicine. Int J Stroke 2011; 6: 328-36.
[41] Hermann DM, Bassetti CL. Sleep-related breathing and sleep-wake disturbances in ischemic stroke. Neurology 2009; 73: 1313-22.
[42] Hackett ML, Yang M, Anderson CS, Horrocks JA, House A. Pharmaceutical interventions for emotionalism after stroke. Cochrane Database Syst Rev 2010: CD003690.
[43] Jiménez I, Sobrino T, Rodríguez-Yáñez M, Pouso M, Cristobo I, Sabucedo M, Blanco M, Castellanos M, Leira R, Castillo J. High serum levels of leptin are associated with post-stroke depression. Psychol Med 2009; 39: 1201-9.
[44] Nickel A, Thomalla G. Post-stroke depression: impact of lesion location and methodological limitations-a topical review. Front Neurol 2017; 8: 498.
[45] Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke 2005; 36: 1330-40.
[46] Fedoroff JP, Starkstein SE, Parikh RM, Price TR, Robinson RG. Are depressive symptoms nonspecific in patients with acute stroke? Am J Psychiatry 1991; 148: 1172-6.
[47] Cole MW, Schneider W. The cognitive control network: integrated cortical regions with dissociable functions. Neuroimage 2007; 37: 343-60.
[48] Grajny K, Pyata H, Spiegel K, Lacey EH, Xing S, Brophy C, Turkeltaub PE. Depression symptoms in chronic left hemisphere stroke are related to dorsolateral prefrontal cortex damage. J Neuropsychiatry Clin Neurosci 2016; [Epub ahead of print].
[49] Egorova N, Cumming T, Shirbin C, Veldsman M, Werden E, Brodtmann A. Lower cognitive control network connectivity in stroke participants with depressive features. Transl Psychiatry 2018; 7: 4.
[50] Carter RM, Huettel SA. A nexus model of the temporal-parietal junction. Trends Cogn Sci 2013; 17: 328-36.

[51] Lim JS, Kang DW. Stroke connectome and its implications for cognitive and behavioral sequela of stroke. J Stroke 2015; 17: 256-67.
[52] Narushima K, Kosier JT, Robinson RG. A reappraisal of poststroke depression, intra-and inter-hemispheric lesion location using meta-analysis. J Neuropsychiatry Clin Neurosci 2003; 15: 422-30.
[53] Wei N, Yong W, Li X, Zhou Y, Deng M, Zhu H, Jin H. Post-stroke depression and lesion location: a systematic review. J Neurol 2015; 262: 81-90.
[54] Flaster M, Sharma A, Rao M. Poststroke depression: a review emphasizing the role of prophylactic treatment and synergy with treatment for motor recovery. Top Stroke Rehabil 2013; 20: 139-50.
[55] Nestler EJ. Treating the brain deep down: brain surgery for anorexia nervosa? Nat Med 2013; 19: 678-9.
[56] Belzung C, Turiault M, Griebel G. Optogenetics to study the circuits of fear-and depression-like behaviors: a critical analysis. Pharmacol Biochem Behav 2014; 122: 144-57.
[57] Margoob MA, Mushtaq D. Serotonin transporter gene polymorphism and psychiatric disorders: is there a link? Indian J Psychiatry 2011; 53: 289-99.
[58] Sacchetti M, Della Marca G. Are stroke cases affected by sleep disordered breathings all the same? Med Hypotheses 2014; 83: 217-23.
[59] Lim CM, Kim SW, Park JY, Kim C, Yoon SH, Lee JK. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. J Neurosci Res 2009; 87: 1037-45.
[60] Capuron L, Pagnoni G, Demetrashvili MF, Lawson DH, Fornwalt FB, Woolwine B, Berns GS, Nemeroff CB, Miller AH. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology 2007; 32: 2384-92.
[61] Krugers HJ, Maslam S, Korf J, Joëls M. The corticosterone synthesis inhibitor metyrapone prevents hypoxia/ischemia-induced loss of synaptic function in the rat hippocampus. Stroke 2000; 31: 1162-72.
[62] Sierra-Johnson J, Romero-Corral A, Lopez-Jimenez F, Gami AS, Sert Kuniyoshi FH, Wolk R, Somers VK. Relation of increased leptin concentrations to history of myocardial infarction and stroke in the US population. Am J Cardiol 2007; 100: 234-9.
[63] Zhang F, Wang S, Signore AP, Chen J. Neuroprotective effects of leptin against ischemic injury induced by oxygen-glucose deprivation and transient cerebral ischemia. Stroke 2007; 38: 2329-36.
[64] Signore AP, Zhang F, Weng Z, Gao Y, Chen J. Leptin neuroprotection in the central nervous system: mechanisms and therapeutic potentials. J Neurochem 2008; 106: 1977-90.
[65] Steiner AA, Romanovsky AA. Leptin: at the crossroads of energy balance and systemic inflammation. Prog Lipid Res 2007; 46: 89-107.
[66] Zhou Z, Lu T, Xu G, Yue X, Zhu W, Ma M, Liu W, Zhu S, Liu X. Decreased serum brain-derived neurotrophic factor (BDNF) is associated with post-stroke depression but not with BDNF gene Val66Met polymorphism. Clin Chem Lab Med 2011; 49: 185-9.
[67] Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, Yoon JS. BDNF genotype potentially modifying the association between incident stroke and depression. Neurobiol Aging 2008; 29: 789-92.
[68] Tong L, Perez-Polo R. Brain-derived neurotrophic factor (BDNF) protects cultured rat cerebellar granule neurons against glucose deprivation-induced apoptosis. J Neural Transm (Vienna) 1998; 105: 905-14.
[69] Williams LS, Ghose SS, Swindle RW. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry 2004; 161: 1090-5.
[70] Karceski S. Suicide after stroke. Neurology 2015; 84: e130-3.
[71] House A, Knapp P, Bamford J, Vail A. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. Stroke 2001; 32: 696-701.
[72] Ayerbe L, Ayis S, Crichton SL, Rudd AG, Wolfe CD. Explanatory factors for the increased mortality of stroke patients with depression. Neurology 2014; 83: 2007-12.
[73] Wu S, Barugh A, Macleod M, Mead G. Psychological associations of poststroke fatigue: a systematic review and meta-analysis. Stroke 2014; 45: 1778-83.
[74] Chun HY, Whiteley WN, Dennis MS, Mead GE, Carson AJ. Anxiety after stroke: the importance of subtyping. Stroke 2018; 49: 556-64.
[75] Menlove L, Crayton E, Kneebone I, Allen-Crooks R, Otto E, Harder H. Predictors of anxiety after stroke: a systematic review of observational studies. J Stroke Cerebrovasc Dis 2015; 24: 1107-17.
[76] Ayerbe L, Ayis SA, Crichton S, Wolfe CD, Rudd AG. Natural history, predictors and associated outcomes of anxiety up to 10 years after stroke: the South London Stroke Register. Age Ageing 2014; 43: 542-7.
[77] Lee JK, Orsillo SM, Roemer L, Allen LB. Distress and avoidance in generalized anxiety disorder: exploring the relationships with intolerance of uncertainty and worry. Cogn Behav Ther 2010; 39: 1 26-36.
[78] Huang CY, Fujimura M, Noshita N, Chang YY, Chan PH. SOD1 down-regulates NF-kappaB

and c-Myc expression in mice after transient focal cerebral ischemia. J Cereb Blood Flow Metab 2001; 21: 163-73.
[79] Nurmi A, Lindsberg PJ, Koistinaho M, Zhang W, Juettler E, Karjalainen-Lindsberg ML, Weih F, Frank N, Schwaninger M, Koistinaho J. Nuclear factor-kappaB contributes to infarction after permanent focal ischemia. Stroke 2004; 35: 987-91.
[80] Zhang X, Polavarapu R, She H, Mao Z, Yepes M. Tissue-type plasminogen activator and the low-density lipoprotein receptor-related protein mediate cerebral ischemia-induced nuclear factor-kappaB pathway activation. Am J Pathol 2007; 171: 1281-90.
[81] Kaushal V, Schlichter LC. Mechanisms of microglia-mediated neurotoxicity in a new model of the stroke penumbra. J Neurosci 2008; 28: 2221-30.
[82] Blondeau N, Widmann C, Lazdunski M, Heurteaux C. Activation of the nuclear factor-κB is a key event in brain tolerance. J Neurosci 2001; 21: 4668-77.
[83] Kaltschmidt B, Kaltschmidt C. NF-kappaB in the nervous system. Cold Spring Harb Perspect Biol 2009; 1: a001271.
[84] Zhu LJ, Ni HY, Chen R, Chang L, Shi HJ, Qiu D, Zhang Z, Wu DL, Jiang ZC, Xin HL, Zhou QG, Zhu DY. Hippocampal nuclear factor kappa B accounts for stress-induced anxiety behaviors via enhancing neuronal nitric oxide synthase (nNOS)-carboxy-terminal PDZ ligand of nNOS-Dexras1 coupling. J Neurochem 2018; 146: 598-612.
[85] Yeh SH, Lin CH, Lee CF, Gean PW. A requirement of nuclear factor-κB activation in fear-potentiated startle. J Biol Chem 2002; 277: 46720-9.
[86] Kassed CA, Herkenham M. NF-κB p50-deficient mice show reduced anxiety-like behaviors in tests of exploratory drive and anxiety. Behav Brain Res 2004; 154: 577-84.
[87] Ahn GE, Ramsey-Goldman R. Fatigue in systemic lupus erythematosus. Int J Clin Rheumtol 2012; 7: 217-227.
[88] Calabrese M, Rinaldi F, Grossi P, Mattisi I, Bernardi V, Favaretto A, Perini P, Gallo P. Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis. Mult Scler 2010; 16: 1220-8.
[89] Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain 2010; 133: 3434-43.
[90] Kirkevold M, Christensen D, Andersen G, Johansen SP, Harder I. Fatigue after stroke: manifestations and strategies. Disabil Rehabil 2012; 34: 665-70.
[91] Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. Nat Rev Neurol 2017; 13: 662-75.
[92] Staub F, Bogousslavsky J. Post-stroke depression or fatigue? Eur Neurol 2001; 45: 3-5.
[93] De Groot MH, Phillips SJ, Eskes GA. Fatigue associated with stroke and other neurologic conditions: implications for stroke rehabilitation. Arch Phys Med Rehabil 2003; 84: 1714-20.
[94] Cumming TB, Packer M, Kramer SF, English C. The prevalence of fatigue after stroke: a systematic review and meta-analysis. Int J Stroke 2016; 11: 968-77.
[95] Kuppuswamy A, Clark EV, Sandhu KS, Rothwell JC, Ward NS. Post-stroke fatigue: a problem of altered corticomotor control? J Neurol Neurosurg Psychiatry 2015; 86: 902-4.
[96] Kuppuswamy A, Clark EV, Turner IF, Rothwell JC, Ward NS. Post-stroke fatigue: a deficit in corticomotor excitability? Brain 2015; 138: 136-48.
[97] Christensen D, Johnsen SP, Watt T, Harder I, Kirkevold M, Andersen G. Dimensions of post-stroke fatigue: a two-year follow-up study. Cerebrovasc Dis 2008; 26: 134-41.
[98] Booij HA, Gaykema WDC, Kuijpers KAJ, Pouwels MJM, den Hertog HM. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury. Endocr Connect 2018; 7: R223-R237.
[99] Helgason CM. Blood glucose and stroke. Curr Treat Options Cardiovasc Med 2012; 14: 284-7.
[100] Kurzepa J, Bielewicz J, Stelmasiak Z, Bartosik-Psujek H. Serum bilirubin and uric acid levels as the bad prognostic factors in the ischemic stroke. Int J Neurosci 2009; 119: 2243-9.
[101] Romanos E, Planas AM, Amaro S, Chamorro A. Uric acid reduces brain damage and improves the benefits of rt-PA in a rat model of thromboembolic stroke. J Cereb Blood Flow Metab 2007; 27: 14-20.
[102] Wu D, Wang L, Teng W, Huang K, Shang X. Correlation of fatigue during the acute stage of stroke with serum uric acid and glucose levels, depression, and disability. Eur Neurol 2014; 72: 223-7.
[103] Hermann DM, Bassetti CL. Role of sleep-disordered breathing and sleep-wake disturbances for stroke and stroke recovery. Neurology 2016; 87: 1407-16.
[104] Hermann DM, Siccoli M, Kirov P, Gugger M, Bassetti CL. Central periodic breathing during sleep in acute ischemic stroke. Stroke 2007; 38: 1082-4.
[105] Dziewas R, Humpert M, Hopmann B, Kloska SP, Lüdemann P, Ritter M, Dittrich R, Ringelstein EB, Young P, Nabavi DG. Increased prevalence of sleep apnea in patients with re-

curring ischemic stroke compared with first stroke victims. J Neurol 2005; 252: 1394-8.
[106] Hermann DM, Siccoli M, Brugger P, Wachter K, Mathis J, Achermann P, Bassetti CL. Evolution of neurological, neuropsychological and sleep-wake disturbances after paramedian thalamic stroke. Stroke 2008; 39: 62-8.
[107] Hui DS, Choy DK, Wong LK, Ko FW, Li TS, Woo J, Kay R. Prevalence of sleep-disordered breathing and continuous positive airway pressure compliance: results in chinese patients with first-ever ischemic stroke. Chest 2002; 122: 852-60.
[108] Selic C, Siccoli MM, Hermann DM, Bassetti CL. Blood pressure evolution after acute ischemic stroke in patients with and without sleep apnea. Stroke 2005; 36: 2614-8.
[109] Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27: 401-7.
[110] Leppavuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T. Insomnia in ischemic stroke patients. Cerebrovasc Dis 2002; 14: 90-7.
[111] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353: 2034-41.
[112] Munoz R, Duran-Cantolla J, Martínez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006; 37: 2317-21.
[113] Palomaki H. Snoring and the risk of ischemic brain infarction. Stroke 1991; 22: 1021-5.
[114] Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. J Sleep Res 2009; 18: 148-58.
[115] Hellman K, Hernandez P, Park A, Abel T. Genetic evidence for a role for protein kinase A in the maintenance of sleep and thalamocortical Oscillations. Sleep 2010; 33: 19-28.
[116] Luo J, Phan TX, Yang Y, Garelick MG, Storm DR. Increases in cAMP, MAPK activity, and CREB phosphorylation during REM sleep: implications for REM sleep and memory consolidation. J Neurosci 2013; 33: 6460-8.
[117] Calvert T, Knapp P, House A. Psychological associations with emotionalism after stroke. J Neurol Neurosurg Psychiatry 1998; 65: 928-9.
[118] House A, Dennis M, Molyneux A, Warlow C, Hawton K. Emotionalism after stroke. BMJ 1989; 298: 991-4.
[119] Kim JS, Choi-Kwon S. Poststroke depression and emotional incontinence: correlation with lesion location. Neurology 2000; 54: 1805-10.
[120] Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying: a link to the cerebellum. Brain 2001; 124: 1708-19.
[121] Kim JS. Post-stroke emotional incontinence after small lenticulocapsular stroke: correlation with lesion location. J Neurol 2002; 249: 805-10.
[122] Andersen G, Ingeman-Nielsen M, Vestergaard K, Riis JO. Pathoanatomic correlation between poststroke pathological crying and damage to brain areas involved in serotonergic neurotransmission. Stroke 1994; 25: 1050-2.
[123] Bingelien A, Shapiro C, Sockalingam S, Hawa R. Pathological Laughing and Crying Post-stroke: Liaison Psychiatrist Beware Clinical Case 2016. pp. 12-3.
[124] Murai T, Barthel H, Berrouschot J, Sorger D, von Cramon DY, Muller U. Neuroimaging of serotonin transporters in post-stroke pathological crying. Psychiatry Res 2003; 123: 207-11.
[125] Moller M, Andersen G, Gjedde A. Serotonin 5HT1A receptor availability and pathological crying after stroke. Acta Neurol Scand 2007; 116: 83-90.