Post-stroke depression and the aging brain

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Abstract

Ageing is associated with changes in the function of various organ systems. Changes in the cardiovascular system affect both directly and indirectly the function in a variety of organs, including the brain, with consequent neurological (motor and sensory performance) and cognitive impairments, as well as leading to the development of various psychiatric diseases. Post-stroke depression (PSD) is among the most frequent neuropsychiatric consequences of cerebral ischemia. This review discusses several animal models used for the study of PSD and summarizes recent findings in the genomic profile of the ageing brain, which are associated with age-related disorders in the elderly. Since stroke and depression are diseases with increased incidence in the elderly, great clinical benefit may especially accrue from deciphering and targeting basic mechanisms underlying PSD. Finally, we discuss the relationship between ageing, circadian rhythmicity and PSD.

Keywords: Aging, Stroke, Post stroke depression, Gene profiling

Review

Background

Depression in stroke survivors is of utmost clinical relevance. It often takes a chronic course and is associated with increased morbidity, mortality and a poorer functional outcome. Despite the fact that a high proportion of stroke patients develop mood symptoms, the pathomechanisms underlying the development of post-stroke depression (PSD) have so far received little attention from the field of neurobiology. Relevant animal models have only sparsely been investigated. This research gap becomes even more regrettable if one considers the growing body of clinical evidence indicating a beneficial effect of antidepressants and especially of selective serotonin reuptake inhibitors (SSRIs), on post-ischemic outcome. Since old age as such is also associated with an enhanced susceptibility to stroke along with a poorer recovery from brain injury, it deserves to be investigated as a key modulatory factor. If we cannot prevent stroke, we shall try to alleviate its long-term consequences. In particular, great clinical benefit may accrue from deciphering and targeting basic mechanisms underlying chronic PSD in aged animals. So far, the majority of experimental stroke studies have concentrated heavily on acute stroke outcome, which, after all, represents only a snapshot of a complex sequence of events. This limitation may have majorly contributed to the conspicuous discrepancy between laboratory and clinical findings that has been a recurrent theme in stroke research in recent years (‘translational road block”).

Post-stroke depression & aging

Age is the most important risk factor for cerebral ischemia and recovery after stroke is significantly influenced by age. A large spectrum of factors, like genetic, epigenetic or environmental factors, contributes to the aging phenotype. One prospective population-based study estimates that the incidence of mental illnesses like anxiety, anhedonia and depression after stroke is about 35% among the stroke survivals and the rate of disabilities and cognitive deficits increased with age [1]. Depression after stroke runs a chronic course and is related to increased morbidity and mortality [2-9]. More than that, depression symptoms may even worsen during the chronic phase after stroke [1,9,10]. Anxiety is associated with physical disability may contribute to the development of PSD. However, the higher prevalence of symptoms of depression in stroke patients as compared with other patients with similar degree of disability can be a good argument against psychological explanations of PSD [9,11].
Comorbidities such as hypertension, obesity, diabetes, dyslipidemia and systemic inflammation increase the probability of silent strokes. Microvascular changes and silent strokes in vulnerable regions may lead to the so-called 'vascular depression' [12,13]. Several genes such as the genes encoding angiotensin-converting enzyme (ACE), protein kinase C (PRKCH), apolipoprotein (a) [apo (a)] and lipoprotein(a) [Lp(a)] may play an important role in the etiology of vascular depression [14-16].

Animal models of stroke and post-stroke depression: role of aging
To study the biological processes underlying functional recovery after stroke in ageing brain a variety of physiologically complex organisms like rats, mice or nonhuman primates have been used. But, the rat model is by far the most used in stroke research due to the similarities with human brain neurovascular branching and the available behavioural outcome measurements. The most commonly used ischemic stroke models in rodents are: middle cerebral artery occlusion (MCAO) for transient or permanent occlusion and endothelin-1 model for transient occlusion. To study the rehabilitation process after cerebral ischemia is important to choose an appropriate animal model and to optimize this model. Epidemiological studies reveal that human ischemic stroke occurs frequently in late middle age (50-70 years) than at older ages (over 70 years) [17,18]. Therefore it is highly recommened to use middle aged rats for stroke studies. Consequently, animal studies conducted on aged (18 month-old) rats demonstrated that there was a decline in the ability of aged brain to sustain plasticity-related process and poorer neurological functional recovery after ischemia in older rats than in younger animals [19-25]. Other research studies that used middle-aged rats (12-18-month) showed that more expressed alteration have been found compared with young animals at structural and functional levels [24,26-29]. Interestingly, there are significant differences in brain response to injury in old subjects compared with young ones. Therefore extrapolating the results from young animals to aged humans could lead to erroneous conclusions.

The aged rodent model offers a useful tool to investigate mechanisms and treatments of ischemic stroke in preclinical studies. The models in aged animals have to be designed to create a reproducible lesion which mimics the human pathophysiological changes, to be minimally invasive, and to allow objective measurement and analysis of tissue damage after cerebral ischemia. In agreement with this concept, previous studies have shown that mortality in post-stroke aged rate is higher compared with young animals, most likely because the lesion appears on a background already altered by senescence itself. On the physiological level, functional and cognitive decline are closely connected to morphological changes of the brain during the aging process.

Imaging techniques, positron emission tomography (PET) or magnetic resonance imaging (MRI), have revealed a significant reduction in the cerebral blood flow (CBF), mostly in the cortex, which may be linked to these morphological changes in the aged brain. Overall, cerebrovascular dysfunction associated with metabolic changes due to senescence increases the vulnerability of brain to ischemic-hypoxic injuries like stroke. Cerebral ischemia occurs frequently in elderly, and increased vulnerability of the aged brain leads to unfavorable recovery of physical and cognitive functions. Although imaging techniques have already been used in numerous studies in animal models of stroke, few groups have applied MRI methods to characterize and monitor the dynamics of ischemic lesions in aged ischemic animals [30-33].

The aged brain displays a higher susceptibility to hypoxia compared with young animals in the acute phase of stroke [27,32]. On MRI images, aged ischemic rats displayed more severe lesions, which were with similar localizations, but higher incidence and more rapid appearance than in the young rats [30,31]. With the use of functional magnetic resonance imaging (fMRI) it was demonstrated that patterns of bihemispheric reorganization (increase of the fMRI response in the ipsilateral somatosensory cortex and bilateral thalamic activation) after permanent MCAO in aged rats were the same as in young animals, although the overall time course of recovery in aged rats was more prolonged than that in young rats [32]. Studies using electrophysiological techniques, and in particular electroencephalography (EEG), in ischemic aged animals are mostly lacking. EEG has been used as a tool for verifying the success of the occlusion [30], for identifying the effect of hypothermia on neuronal functions [34].

Animal models of depression
Modelling psychiatric conditions like depression after stroke in animal models is not trivial. The psychological evaluation by clinicians is not available in animal models and most of these models are validated only by behavioural observation or by behavioural changes in response to treatment. Therefore instead of trying to fully replicate all the human symptoms of depression, we shall try to uncover the underlying signalling pathways in animal models of mood disorders that strongly meet the validating criteria including strong endophenotype similarities, comparable etiology and the same treatment [35-37]. To this end, various behavioral tests have been proposed to investigate some of the central aspects of human-like depression in rodents. For example, the forced swim test in which rodents are exposed to water stress and are
forced to swim [9,38] or the tail suspension test (animals are suspended horizontally by tail for a short period of time) [39,40] are commonly used as behavioral paradigms that quantify behavioral changes in a stressful situation (behavioral despair). These tests measure the immobility of depressed animals in despair situation and have been pharmacologically validated using antidepressant drugs that are already in human use [41,42].

Anhedonia (the loss of interest) is an important symptom of depression that can be measured in rodents by a decrease in sucrose consumption. Rodents normally prefer sweet fluids like glucose or sucrose instead of water. Quantifying consumption of sucrose is the most used endpoint for assessing motivation and affective state in rodents after repeated chronic stress exposure. Also, this test can quantify reversal of this effects after antidepressive drugs administration [9,43-45]. Some studies report decreased sucrose consumption at 2 weeks after transient focal ischemia in mice, suggesting a hedonic deficit in MCAO animals [40,44-46].

Exposure to unpredictable chronic mild stress (CMS) associated with isolation of animals after ischemia is another way to study experimental PSD. It has been shown that after cerebral ischemia, animals show decreased locomotor activity in the open field test and decreased sucrose consumption when exposed to CMS paradigm for 18 days after surgery [9].

Biology of post-stroke depression: role of ageing

The high incidence rates of stroke patients that develop mood symptoms (between 20-50%) justify the effort of researchers to go further into the neurobiological mechanisms of disease [47-49]. Many studies suggest that PSD is a consequence of brain lesions that are associated with disruptions in synaptic transmission, changes in signalling pathways and increased biological vulnerability of the post-stroke aged brain [50-53]. Some other studies reported that PSD is a consequence of specific brain lesions and differences in the incidence of depression between different brain areas have been reported [54,55]. In this context, left hemispheric cortical stroke, mainly frontal lesions has been reported to be linked with an increased risk for depression. However, there are still controversial points of view regarding the relationship between the area of the brain affected by stroke and incidence of PSD.

On the other hand, the prevalence of the memory cognitive impairment like dementia or depression is higher in elderly after stroke. One question is that if cerebral ischemia causes secondary degenerative changes in the brain or that ongoing degenerative changes will be simply aggravated by stroke. From a psychological perspective, the severity of PSD is determined not only by individual differences in emotional reactions to disease (e.g. negative attitude) but also, by the severity of physical and cognitive impairment and by the absence of familial and social support [56].

Many studies suggest that post-stroke vulnerability of the brain can induce PSD and PSD is associated with reduced recovery after stroke in stroke survival patients. However, until now there is no clear evidence to support the etiological mechanisms of PSD, which seems to be a multifactorial disease of the ageing brain.

One important issue is how to distinguish the depressive symptoms in patients in the early stages after stroke from cognitive impairments due to neurodegeneration prior to stroke and the ageing process itself. Some longitudinal studies on post stroke patients showed that chronic PSD is highly predictable if post stroke patients are experiencing depression symptoms between 6 month and 1 year after brain injury [57,58].

Most of these studies analyzed the risk of post-stroke depression in relatively young people’s that have a job and are not living alone. Also, in these studies, patients with language problems like aphasia or neurodegenerative disease like dementia were excluded. However, since stroke occur frequently in people over 65, studies on older patients with stroke and other age-related comorbidities should be more relevant than studies on young people. In this light, multi-therapeutic approach of PSD in the recovery phase that include genetic, social and psychological aspects have the greatest potential for improving post-stroke recovery and the quality of life in elderly post-stroke survivors.

Neurogenesis, cognitive decline & post-stroke depression

Age-related cognitive decline is often associated with decreased hippocampal neurogenesis and depression, but relatively little is known about the biological significance of neurogenesis in the ageing mammalian brain for the development of depression. Two major hypotheses have driven most of the studies on hippocampal neurogenesis, namely (i) it plays a pivotal role in hippocampus-dependent learning and memory [59,60] and, (ii) it protects against anxiety and depression [61,62]. However, mechanisms underlying the precise role of neurogenesis remains controversial. For example, genetic ablation of the cell cycle regulatory protein cyclin D2 that results in virtual absence of newly born neurons in the adult brain does not lead, surprisingly, to appreciable learning and memory deficits [63-65]. Similarly, the involvement of hippocampal neurogenesis in depression and in the efficacy of antidepressive treatments is also not fully understood.

One possible molecular mechanism underlying age-related depression and decreased neurogenesis can be due to an increased level of the dickkopf 1 homolog - Xenopus laevis (Dkk1), that decreases Wnt signaling
pathways and has been associated with a decline in hippocampal neurogenesis [66].

Other mechanisms that can be involved in neurorecovery are related to neurotrophin signaling pathway. Neurotrophins are important players in early neuronal gene response to injuries. The neurotrophin-signaling pathway activates extracellular-signal-regulated kinases (ERK) pathway and nuclear transcription. Meier and colleagues demonstrated that hippocampal neuronal culture treated with brain derived neurotrophic factor (BDNF) promotes axonal guidance, modulate the synaptic function, stimulate neurite branching and is antagonized by Ephrin (Eph) signaling [67,68]. Also, decreased levels of BDNF, a key factor in the regulation of hippocampal neurogenesis, seems to be associated with depression and neurodegenerative disorders, but the mechanisms underlying this association are still unknown [69]. Finally, Cui and colleagues reported that the combination therapy, simvastatin with human umbilical blood cells, increased endogenous neurogenesis and cell plasticity in the ischemic area via BDNF/TrkB signaling pathway [70].

Even less is known about the relationship between PSD and neurogenesis in the elderly. The level of hippocampal neurogenesis has been shown to decrease steadily with aging [71]. Since aged animals might be both more prone to develop a depressive phenotype [72] and the aged brain is more sensitive to the deleterious effects of ischemia [27,73], one could expect more severe PSD symptoms in aged animals. Such an experimental model of PSD, taking into account these influences of aging, should be highly clinically relevant.

Depressive behavior in ischemic rats was accompanied by reduced ischemia-evoked hippocampal neurogenesis and this effect was reversed by citalopram administration [9]. Using pharmacological interventions, the involvement of serotonergic neurotransmission was then further corroborated [74,75]. One study in non-human primates, proved that the repeated separation stress is associated with depression-like behavior (anhedonia) and reduced hippocampal neurogenesis [76]. Also, recovery from stroke was shown to be associated with growth factor-induced neurogenesis in SVZ as well as exercise-induced neurogenesis in SGZ [77,78]. Similarly, therapy with granulocyte colony stimulating factor (G-CSF) enhanced neurogenesis, improved working memory in the radial-arm maze test and in consequence the survival capacity and functional outcome after stroke [27]. However, these findings need further confirmation along with a clear demonstration of functional significance in human diseases. We should take into account that other age-associated comorbidities like hypertension or obesity can negatively affect the hippocampal functions.

**Genome profiling of mood disorders in the elderly**

Transcriptional profiling is a useful tool to identify genetic pathways associated with mood symptoms in the elderly. Most studies reporting the use of gene expression profiling to investigate rodent models of depression focused on stress models and did not supply direct evidence for a specific genomic signature in PSD depression. Kang and colleagues identified some synaptic-function-related genes that are connected with decreased in number and function of synapse in a rat model of major depression. These genes included: calmodulin 2 (Calm2), synapsin 1 (Syn1), tubulin beta 4 (Tubb4) a member of ras-related protein Rab-4B (Rab4b). Also, increased expression of the transcriptional repressor erythroid transcription factor GATA-binding factor 1 (GATA1) is responsible for down-regulation of these synaptic-function-related genes [79].

In another study, genes related to human major depression like serotonin receptor 2a gene (Htr2a), neurotrophic tyrosine kinase receptor type 2 and 3 genes (Ntrk2 and Ntrk3), corticotropin releasing hormone receptor 1 (Crhrl) and corticotropin releasing hormone (Crh) were differentially expressed in three animal models of depression: acute treatment with reserpine, olfactory bulbectomy and chronic treatment with corticosterone [9]. In addition, two new genes, complement component 3 and fatty acid-binding protein 7, have recently been described [80,81]. Similarly, polymorphism of 5- hydroxytryptamine 2a receptor (Htr2a), a postsynaptic target for serotonin signaling, has been implicated in neuropsychiatric disorders [82]. In addition, increased functional activity of the amygdala in response to negative stimuli appears to be a mood-congruent phenomenon that is likely moderated by the 5-HT transporter gene (Slc6a4) promoter polymorphism (5-Httlpr) [9]. Lohon and colleagues showed significant gene-gene interaction between Slc6a4 and 5-Httlpr/ rs25531 in general anxiety disorder [83]. An oligodendrocyte/myelin-associated genes, 2,3’-cyclic nucleotide 3’-phosphodiesterase (CNP) was identified to be associated with catatonia-depression syndrome in the elderly. Using aged heterozygous null mutant mice model of spontaneous catatonia, Hagemeyer and colleagues showed that the reduced expression of CNP is accelerated by aging and is associated with neurodegenerative changes in the elderly [84].

**Gene expression & mood disorders in elderly**

In previous studies we have identified a number of genes that are involved in neuropathic syndrome and PSD signaling pathways in aged brain (e.g. 5- hydroxytryptamine 2a receptor - Htr2h, prepronociceptin - Pnoc). These genes could be pharmacological targets in a multimodal therapy of stroke and stroke related diseases [16].
Using fosB-Null mice, Yutsudo and colleagues reported impaired neurogenesis and depressive behavior in fosB-Null mice [85]. Intriguingly, FBJ murine osteosarcoma viral oncogene homolog B (fosB) expression has been associated with stem cell and neural progenitor cells proliferation after cerebral ischemia in mammalian central nervous system [86,87]. These studies suggest the genomic signature is crucial for the evolution of disease, but is the "genomic reprogramming" a future powerful tool that can be exploited to improve the neurorecovery after stroke? Some studies identified the ciliary neurotrophic factor (Cntf) receptor as a key molecular factor that can inhibit neurogenesis in the type B stem cells, but the mechanism is still unknown [88,89]. Cntf is expressed only in central nervous system where modulates the normal neurogenesis. Stimulation of this factor can be a novel pharmaceutical strategy for neurogenesis-dependent diseases like stroke and PSD [89].

Table 1 summarize all the specific genes involved in the etiology of depression and post-stroke depression.

### Mood disorders, circadian rhythmicity and aging
Disturbances in the circadian rhythm may have dramatic effects on our health. Changes in biological rhythm disturbances precede and parallel the occurrence of mood episodes of illness and have been proposed to play a pathogenetic role in major depression and mania [105-110]. The controlled administration of stimuli that

| Gene symbol | Description | Gene Function | Gene expression | Disease | Human/animal data | Ref. |
|-------------|-------------|---------------|----------------|---------|--------------------|------|
| **Depression** | | | | |
| GSK-β | Synthase-kinase-3β | Central regulator of circadian rhythms | Up | Depression | Transgenic mice | [90] |
| CLOCK | Circadian Locomotor Output Cycles Kaput | Central regulator of circadian rhythms | SNP | DepressionBipolar disorders | Transgenic mice | [91] |
| ARNTL (BMAL1) | Aryl hydrocarbon receptor nuclear translocator-like | PER1 activator | SNP | Sleep disorders | Human sample, | [92,93] |
| NPAS2 | Neuronal PAS domain protein 2 | Part of a molecular clock | SNP | Mood disorders | Human sample, | [92,94] |
| **Synapse-related genes in depression** | | | | |
| CALM2 | Calmodulin 2 | Cytokinesis regulator | Down | Depression | Animal model | [89] |
| SYN1 | Synuclein1 | Synaptogenesis and neurotransmitter release | Down | Depression | Animal model | [89,95] |
| **Depression in the elderly** | | | | |
| PER2 | Period circadian clock 2 | Central regulator of circadian rhythms | SNP | Sleep disorders | Human sample Animal model of ageing | [92,93,96] |
| PER3 | Period circadian clock 3 | Central regulator of circadian rhythms | SNP | Sleep disorders, Aged brain | Human sample | [93,97-99] |
| S-HTTLPR | Serotonin transporter promoter | Serotonin transporter | SNP | Depression in the elderly | Human sample | [100] |
| TUBB4 | Tubulin, Beta 4A Class IVa | Constituent of microtubules | Down | Depression | Ageing | Animal model | [89,101] |
| **Depression and recovery after stroke** | | | | |
| BDNF | Human brain-derived neurotrophic factor (BDNF) | Growth factor in the brain | SNP | Depression Recovery after injury | Human sample, Animal model | [102,103] |
| SLC6A4 | Solute Carrier Family 6 Member 4 | Membrane protein transporter of serotonin | SNP | Depression Stroke recovery | Human sample | [9,83] |
| GATA1 | GATA Binding Protein 1 | Transcription factors | Upregulation | Depression Stroke recovery | Animal model | [104] |
| HTR2B | 5-Hydroxytryptamine (Serotonin) Receptor 2B | Serotonin receptor | Upregulation | Poststroke depression in elderly | Animal model | [16,34] |
| PNOC | Prepronociceptin | Opioid receptor | Downregulation | Poststroke depression in elderly | Animal model | [16,34] |
Circadian rhythms display an unregular pattern with aging manifested by alteration of sleep quality and cognitive performance [119,120]. Hermannn and Bassetti [121] showed that the alterations of the sleep-wake cycle like hypersomnia or excessive daytime sleepiness occur in 10%-50% of all stroke cases and are associated with negative long-therm clinical outcome. Also, Ramar and Surani [122] showed that the circadian rhythm disorders could increase the risk of stroke. But, if disturbances in the circadian rhythm are a risk factor or a consequence of ischemic stroke in the elderly remains to be clarified.

Some studies showed that one mechanism that contributes to increased risk of depression is the decrease in the synthesis of N-acetylserotonin with ageing [123]. Since N-acetylserotonin activates TrkB signaling pathway in a circadian fashion (higher in the night and lower during the day) via TrkB receptor, and has antidepressant effects [124] it has been hypothesized that disturbances in the circadian rhythms may cause psychiatric disorders. For example, Bunney and colleague showed that an altered circadian function and altered expression of the central circadian clock genes, BMAL1/CLOCK (Npas2) in mood disorders [125]. Also, Circadian Locomotor Output Cycles Kaput (CLOCK) genes are strongly involved in the circadian rhythm and these are closely related with external factors [126]. Therefore dysfunctions of circadian time regulatory mechanisms in the aged brain may underlie the etiology of PSD in the elderly. The effect of circadian rhythm on PSD outcome in the elderly is still an unexplored field.

**Therapy of post-stroke depression**

Norepinephrine (NE), serotonin (5-HT), and dopamine (DA) overlap in the brain and all three transmitters are implicated in the symptoms of depression Depressive symptoms may result from dysfunction of any or all of the monoamine neurotransmitter systems. The effects of NE, 5-HT and DA overlap in the brain and all three transmitters are implicated in the symptoms of depression. Because these monoamine transporters (MATs) are important regulators of the extracellular neurotransmitter concentration, mouse gene knockouts of serotonin transporter (SERT), the noradrenaline transporter (NAT) and also the dopamine transporter (DAT) located in the plasma membrane of corresponding neurons provide interesting models for possible effects of chronic antidepressant treatments. Inhibition of neurotransmitter reuptake by drugs acting at SERT, NET and/or DAT can produce antidepressant effects [127,128].

The mechanism of PSD was suggested to involve multiple pathways, like immune activation, hypoxia, apoptosis and necrosis of neuronal or glial cells or hyperactivation of the hypothalamic-pituitary-adrenal axis. Many studies
reported different therapeutic strategies designed to improve the PSD outcome. Of these, cortisol-lowering therapies and increases of neurotrophic factors like BDNF were reported to be novel possible therapeutic strategy for PSD [129].

In addition, a growing body of evidence indicate a beneficial effect of antidepressants and especially of SSRIs on postischemic outcome [9]. Antidepressants may also exert direct actions on the brain, providing neuroprotection and promoting brain plasticity and neurogenesis.

Antidepressants treatment initiated soon after stroke in non-depressed post-stroke patients may prevent the later PSD but the time window of treatment remains to be optimized [130]. A number of studies have also reported beneficial effects of antidepressant pharmacotherapy on long-term functional outcome after stroke including activities of daily living as well as cognitive functioning [9,131-135]. Other in vivo and in vitro studies have shown that fluoxetine and paroxetine which are the most commonly prescribed antidepressants, prevented degeneration of nigrostriatal dopaminergic neurons. These drugs reversed the hypoactivation found in the primary motor cortex of patients [136] and the increased activation was correlated with improved performance after drug intake and repression of proinflammatory markers [9]. These results remain, however, to be validated in large clinical trials of stroke patients.

Conclusions
In conclusion, depression is the most frequent neuropsychiatric disease of brain ischemia, affecting up to 35% of all such patients. PSD is associated with negative outcome of functional recovery, cognition and social reintegration of stroke patients. During de past decade, significant efforts have been made to establish an efficient treatment of PSD in the elderly. So far, preclinical and translational research on PSD is largely lacking. The implementation and characterization of suitable animal models is clearly a major prerequisite for deeper insights into the biological basis of post-stroke mood disturbances and may also pave the way for the discovery of novel therapeutic targets. Nevertheless it is unlikely that monotherapies will provide a cure for PSD. Rather multitherapeutic strategies should be at the focus of future clinical trials conducted on PSD and mood disorders patients without cerebral ischemia that show the same clinical profile. In this light, future research is needed to identify the molecular mechanism of disease and to establish the pathways that are modulated by antidepressant drugs leading to a better cognitive recovery in the elderly patients.

Authors’ contribution
AMB conducted the literature search and drafted the manuscript, GRC have made substantial contributions to conception and design, ECS and LB have made contributions to conception and design, APW participated in drafting the manuscript and provided critical revision of the manuscript. All authors read and approved the final manuscript.

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References
1. Wolfe CD, Crichton SL, Heuschmann P, McKevitt CJ, Toschke AM, Grieve AP, Ridd AG: Estimates of outcomes up to ten years after stroke: analysis from the prospective South London stroke register. PLoS Med 2011, 8(5):e1001033.
2. Morris PL, Robinson RG, Andziolewski P, Samuelis J, Price TR: Association of depression with 10-year post-stroke mortality. Am J Psychiatry 1993, 150:124-129.
3. Downhill JE Jr, Robinson RG: Longitudinal assessment of depression and cognitive impairment following stroke. J Neurol Ment Dis 1994, 182(8):425-431.
4. Paolucci S, Antonucci G, Pratesi L, Traballoni M, Grasso MG, Lubich S: Post-stroke depression and its role in rehabilitation of inpatients. Arch Phys Med Rehabil 1999, 80(9):985–990.
5. Gainotti G, Antonucci G, Marra C, Paolucci S: Relation between depression after stroke, antidepressant therapy, and functional recovery. J Neurol Neurosurg Psychiatry 2001, 71(2):258–261.
6. Williams LS, Ghose SS, Swindle RW: Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry 2004, 161(6):1090–1095.
7. Pohjasvaara T, Vatasa R, Leppävuori A, Kaste M, Erkinjuntti T: Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol 2001, 8(4):315–319.
8. Chemerinski E, Robinson RG, Kosier JT: Improved recovery in activities of daily living associated with remission of post-stroke depression. Stroke 2001, 32(11):113–117.
9. Loubinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, Filipkowski RK, Kaczmarek L, Popa-Wagner A: Post-stroke depression: mechanisms, translation and therapy. J Cell Mol Med 2012, 16(8):1961–1969.
10. Hackett ML, Yapa C, Parag V, Anderson CS: Frequency of depression after stroke: a systematic review of observational studies. Stroke 2005, 36(8):1330–1340.
11. Folstein MF, McHugh R, McHugh PR: Mood disorder as a specific complication of stroke. J Neurol Neurosurg Psychiatry 1977, 40(10):1018–1020.
12. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charison M: “Vascular depression” hypothesis. Arch Gen Psychiatry 1997, 54(10):915–922.
13. Charidimou A, Wening DJ: Cerebral microbleeds and cognition in cerebrovascular disease: an update. J Neurol Sci 2012, 321(1–2):50–55.
14. Lim JS, Kwon HM: Risk of “silent stroke” in patients older than 60 years: risk assessment and clinical perspectives. Clin Interv Aging 2010, 5:239–251.
15. Sun MK, Alkon DL: Activation of protein kinase C isoforms for the treatment of dementias. Adv Pharmacol 2012, 64:273–302.
16. Bega AV, Vintilescu R, Balan AT, Popi OT, Streba C, Toescu E, Popa-Wagner A: Repeated PTZ treatment at 25-day intervals leads to a highly efficient accumulation of doublecortin in the dorsal hippocampus of rats. PLoS One 2012, 7(8):e39902.
17. Feigin VL, Lawes CM, Bennett DA, Anderson CS: Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. The LANCET Neurology 2003, 2:433–43.

18. Mishra NK, Diener HC, Lyden PD, Bluhmki E, Lees KR: Influence of age on outcome from Thrombolysis in Acute Stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTAT). Stroke 2010, 41:2641–2648.

19. Wagner AP, Schmoll H, Badan I, Platt D, Kessler C: Brain plasticity: to what extent do aged animals retain the capacity to coordinate genetic activity in response to acute challenges. Exp Gerontol 2000, 35(9–10):1211–1227.

20. Badan I, Buchhold B, Hamm A, Gratzi M, Walker LC, Platt D, Kessler C, Popa-Wagner A: Accelerated glial reactivity to stroke in aged rats correlates with reduced functional recovery. J Cereb Blood Flow Metab 2003, 23(7):845–854.

21. Wang RY, Wang PSC, Yang YR: Effect of age in rats following middle cerebral artery occlusion. Gerontology 2003, 49:27–32.

22. Zhang L, Zhang RL, Wang Y, Zhang C, Zhang ZG, Meng H, Chopp M: Functional recovery in aged and young rats after embolic stroke: treatment with a phosphodiesterase type 5 inhibitor. Stroke 2005, 36:847–852.

23. Won SJ, Xie L, Kim SH, Tang H, Wang Y, Mao X: Age-related decrease of striatal neurogenesis is associated with apoptosis of neural precursors and newborn neurons in response to fibroblast growth factor-2 treatment in a rat model of cerebral artery occlusion. J Neurosci 2003, 23(21):847–852.

24. Chen Y, Sun FY: Age-related decrease of striatal neurogenesis is associated with apoptosis of neural precursors and newborn neurons in rats after brain ischemia. Brain Res 2007, 1169:169–174.

25. DiNapoli VA, Huber JD, Houser K, Li X, Rosen CL: Early disruptions of the blood–brain barrier may contribute to exacerbated neuronal damage and prolonged functional recovery following stroke in aged rats. Neurobiol Aging 2008, 29:753–764.

26. Badan I, Platt D, Kessler C, Popa-Wagner A: Temporal dynamics of degenerative and regenerative events associated with cerebral ischemia in aged rats. Gerontology 2003, 49(6):336–345.

27. Popa-Wagner A, Badan I, Walker L, Groppa S, Patrana N, Kessler C: Accelerated infant development, cytoprotection and apoptosis following transient cerebral ischemia in aged rats. Acta Neuropathol 2007, 113(3):277–293.

28. Karki K, Knight RA, Shen LH, Kapke A, Lu M, Li Y, Chopp M: Age-dependent MRI-detected lesions at early stages of transient global cerebral artery occlusion. J Cereb Blood Flow Metab 2005, 25(7):1080–1087.

29. Narushima K, Kosier JT, Robinson RG: Accelerated glial reactivity to stroke in aged rats. Exp Gerontol 2003, 38:1293–1301.

30. Rashid N, Clarke C, Rogish M: Post-stroke depression and expressed vulnerability to stroke. J Biomed Science 2010, 17:113.

31. Canese R, Lorenzini P, Fortuna S, Volpe MT, Giannini M, Podo F, Michalek H: Age-dependent MR-detected lesions at early stages of transient global ischemia in rat brain. MAGMA 2004, 17:3–6:109–116.

32. Markus TM, Tsai SY, Bollnow MR, Farrer RG, O’Neill TE, Kindler-Baumann DR, Rausch M, Rudin M, Wessner C, Mir AK, Schwab ME, Kartje GL: Recovery and brain reorganization after stroke in adult and aged rats. Ann Neurol 2005, 58:950–953.

33. Macri MA, D’Alessandro N, Di Giulio P, Di Iorio P, Di Luzzo S, Giuliani P, Esposto L, Polsomi K: Region-specific effects on brain metabolites of hypoxia and hyopxia-overflow on cerebral ischemia in young and old rats: a quantitative proton magnetic resonance spectroscopy study. J Biomed Science 2010, 17:14.

34. Joseph C, Buga AM, Vintilescu R, Balseanu AT, Moldovan M, Junker H, Walker L, Lotze M, Popa-Wagner A: Prolonged gaseous hyperthermia prevents the upregulation of phagocytosis-specific protein annexin 1 and causes low-amplitude EEG activity in the aged rat brain after cerebral ischemia. J Cereb Blood Flow Metab 2012, 32(8):1632–1642.

35. Willner P, Mitchell PJ: The validity of animal models of predisposition to depression. Behav Pharmacol 2002, 13:169–188.

36. Vollmay B, Mahleittd MM, Henn FA: Neurogenesis and depression: what animal models tell us about the link. Eur Arch Psychiatry Clin Neurosci 2007, 257:300–303.
62. Sakata K, Martin JR, Duke SM, Vail MG, Overacre AE, Dong BE, Jha S: Effects of antidepressant treatment on mice lacking brain-derived neurotrophic factor expression through promoter IV. *Eur J Neurosci* 2013, 37(11):1863–1874.

63. Kato M, Iwata H, Okamoto M, Iishi T, Nárta H: Focal cerebral ischemia-induced escape deficit in rats is ameliorated by a reversible inhibitor of monoamine oxidase-a: implications for a novel animal model of post-stroke depression. *Eur J Pharmacol* 2000, 336:303–40.

64. Jaholkowski P, Kiryk A, Jedynak P, Ben Abdallah NM, Knapska E, Kowalczyk L: Treatment of stroke with simvastatin and human umbilical cord blood cells: neurogenesis, synaptic plasticity, and axon growth. *Neurosci Lett* 2012, 510:235–239.

65. Jedynak P, Jaholkowski P, Woźniak G, Sandi C, Kaczmarek L, Filipkowski RK: Lack of cyclic D2 impairing adult brain neurogenesis alters hippocampal-dependent behavioral tasks without reducing learning ability. *Behav Brain Res* 2012, 227(1):159–166.

66. Selb DR, Corsini NS, Ellwanger K, Plass C, Mateos A, Pitzer C, Nehrs C, Ceñkeli T, Martin-Villalba A: A loss of dickkopf-1 restores neurogenesis in old age and counteracts cognitive decline. *Cell Stem Cell* 2013, 12:2204–214.

67. Meier C, Anastasiadou S, Knöll B: Cytokines: A potential role of interleukin-1 in the pathogenesis and treatment of sleep disorders. *J Mol Neurosci* 2013, 51:227–235.

68. Cronier BA, Jackson MC, Bruno Garza JL, Trinh DS, Mason CO, Suey, An Y, Maudie, S, Fumetti L, Mattson MP, Reineck E: Plasmapheresis is associated with age-related white matter atrophy but not with cognitive function in older, non-demented adults. *PLoS One* 2012, 7:e43217.

69. Cui X, Chopp M, Shehadah A, Zacharek A, Kuzmin-Nichols N, Sanberg CD: Ischemic injury to white matter: an age-dependent process. *PLoS One* 2013, 8:e59865.

70. Kronenberg G, Balkaya M, Prinz V, Gertz K, Ji S, Kirste I, Heuser I, Kampmann B, Hellmann-Regen J, Gass P, Sohr R, Hellweg R, Waeber C, Juckel G, Sánchez-Cabo F, Dopazo A, Díez Celikel T, Martin-Villalba A: Lack of cyclin D2 impairing adult brain neurogenesis alters hippocampal neurogenesis for the therapeutic action of antidepressants in mice, a model for Alzheimer disease. *Neurobiol Aging* 2012, 33(1):124–125.

71. Yutsudo N, Kamada T, Kajita K, Nomura H, Katoji A, Nohshi YH, Nohshi YN, Takase KI, Sakumi K, Shigeto H, Nakaikeppu Y: fosb-Null Mouse Display Impaired Adult Hippocampal Neurogenesis and Spontaneous Epilepsy with Depressive Behavior. *Neuropsychopharmacology* 2012, 37(5):895–906.

72. Hedgesen T, Leah JD: Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Res Rev* 1998, 28(3):370–400.

73. Kindy MS, Carney JP, Dempsey RJ, Carney JM: Ischemic induction of proenkephalin gene expression in gerbil brain. *J Mol Neurosci* 1991, 2(4):217–228.
Towards a dynamical network view of brain ischemia and cognitive deficits.

Fragmentation of the rest-activity rhythm correlates with age-related impairment and depression.

Disruption of the circadian timing systems: molecular mechanisms in mood disorders. CNS Drugs 2009, 23(Suppl 1):40–52.

Circadian rhythms and depression: human rhythms from daily behavior to hormonal transport. Eur J Pharmacol 2003, 2010(2):240–318.

Circadian rhythm disturbances in post stroke: a review. J Neurol 2010, 256(Suppl 16):1313–1318.

Neuroimaging Markers in Depression after Stroke. J Stroke Cerebrovasc Dis 2012, 21(10):1569–1576.

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