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Review Article

Models of poststroke depression and assessments of core depressive symptoms in rodents: How to choose?

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ABSTRACT

Our previous studies have indicated that depression and declined cognition have been involved in some neurodegenerative diseases including Stroke, Parkinson's diseases and Vascular Parkinsonism. Post-stroke depression (PSD) is the most common psychiatric disorder following a stroke and has high morbidity and mortality. Studies on PSD are increasingly common, but the specific mechanisms remain unknown. Current research mainly includes clinical and animal aspects. Questionnaires and peripheral blood examination are two of the most common methods used to study clinical PSD. The results of questionnaires are influenced by multiple factors such as disease history, education background, occupation, economic status, family relationships and social support. There are certain limitations to blood sample testing; for example, it is influenced by cerebrovascular diseases and some other disruptions of the internal environment. It is difficult for either method to fully clarify the pathophysiological mechanism of PSD. Animal models provide alternative methods to further understand the pathophysiological mechanisms of PSD, such as the involvement of neuronal circuits and cytokines. More than ten animal models of PSD have been developed, and new models are constantly being introduced. Therefore, it is important to choose the appropriate model for any given study. In this paper, we will discuss the characteristics of the different models of PSD and comment on the advantages and disadvantages of each model, drawing from research on model innovation. Finally, we briefly describe the current assessment methods for the core symptoms of PSD models, point out the shortcomings, and present the improved sucrose preference test as a rational evaluation of anhedonia.

Abbreviations: 5-HT, 5-hydroxytryptamine; BBB, Blood-brain-barrier; BD, Behavioral despair; BDNF, Brain-derived nerve growth factor; BDT, Behavioral despair test; CSVD, Cerebral small vessel disease; Cys C, Cystatin C; CI, Chemical induction; CUMS, Chronic unpredictable mild stress; DV, Dorsoventral; EI, Environmental induction; ESI, Electrical stimulation induction; ET-1, Endothelin-1; FST, Forced swimming test; GI, Genetic induction; Hcy, Homocysteine; HPA, Hypothalamic-pituitary-adrenal; LH, Learned helplessness; LR, Long-recovery; MCA, Middle cerebral artery; MCAO, Middle cerebral artery occlusion; ML, Medial–lateral; mPFC, Medial prefrontal cortex; MRI, Magnetic resonance imaging; NSFT, Novelty-suppressed feeding test; OFT, Open field test; PSD, Post stroke depression; PSP, Progressive supranuclear palsy; SI, Surgical induction; SIT, Social interaction test; SR, Short-recovery; SSI, Social stress induction; SPT, Sucrose preference test; TLR-4, Toll-like receptor 4; TST, Tail suspension test; TTC, 2,3,5-triphenyltetrazolium chloride

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1. Introduction

Our previous studies have indicated that cognitive dysfunctions including depression and cognitive impairment have seriously influenced neurological diseases such as Stroke, Cerebral small vessel disease (CSVD), Parkinson's diseases, Vascular Parkinsonism and Progressive supranuclear palsy (PSP) (Bernhardt et al., 2018; Wang et al., 2008a; Wang et al., 2017b; Weng et al., 2018; Xu et al., 2015; Xu et al., 2012; Yenari et al., 2000; Zou et al., 2018; Zou et al., 2017). Poststroke depression (PSD) is the most common psychiatric disorder following a stroke. PSD refers to persistent depressive affect after stroke; this psychiatric condition is characterized by anhedonia, low mood, cognitive impairment, and learning and memory disability (Hachinski, 1999; Robinson and Jorge, 2016; Shetty et al., 2019). PSD has an incidence of 17.93%~42.0% from 2 weeks to 6 months after stroke (Yang et al., 2016; Zhang et al., 2016), seriously affecting the process and outcome of rehabilitation and increasing patients' disability rate. Elderly patients have a higher prevalence of PSD, even last up to 20 months (Eriksson et al., 2015; Popa-Wagner et al., 2014; Salinas et al., 2017; Tang et al., 2018). The 10-year mortality of PSD patients was 3.4 times the overall average for stroke patients (Pietra Pedroso et al., 2016).

Existing antidepressant drugs, including selective serotonin reuptake inhibitors and tricyclic antidepressants, are widely used and exert beneficial effects in patients with neurological diseases such as Alzheimer's disease, Parkinson's disease, and PSD; however, 20% to 30% of patients fail to respond fully to antidepressant treatment (Li et al., 2019a; Shetty et al., 2019; Sun et al., 2018; Villa et al., 2018; Wang et al., 2017a). This is partially due to a lack of understanding of the specific pathophysiological mechanisms of PSD (Villa et al., 2018). Exposure to various exogenous factors (such as economic status, education, family support and social environment) and/or endogenous factors (such as aging, perfusion deficits, brain circuits, neuroendocrine activity, neurochemistry, neurotransmitters and inflammatory cytokines) are thought to contribute to the pathogenesis of PSD, but the exact mechanisms are not completely understood (Popa-Wagner et al., 2014; Robinson and Jorge, 2016; Sarkar et al., 2019; Villa et al., 2018; Zou et al., 2017). Currently, the most common methods for clinical studies of PSD are questionnaires and examination of peripheral blood samples (Liu et al., 2017; Meng et al., 2017; Xu et al., 2018). Questionnaire-based assessments reflect the influence of exogenous factors on PSD patients, while blood tests are affected by multiple factors, such as infection, heart disease and other disordered internal states. Therefore, it is difficult to fully understand the pathophysiological mechanisms affecting brain tissue in patients with PSD. Studies of animal models could be an alternative option, helping reveal and clarify the mechanisms related to PSD. However, the pathogenesis of PSD is complicated, and there are various animal models of PSD, with unique characteristics for each model.

In this review, we summarize the literature to date regarding animal models of PSD and the assessment of its core symptoms. Given that most current PSD studies are based on the general depression model, we will briefly describe the common depression models and then focus on some other PSD models. To evaluate whether a model is successful, the academic community applies three principles: face validity (similarity of clinical characteristics), construct validity (duplication of pathophysiological processes) and predictive validity (sensitivity to the interventions) (Narayanan and Chattarji, 2010; Wang et al., 2017a).

2. Depression model

Since the establishment of the experimental canine depression model by American psychologist Seligman in 1967 (Seligman et al., 1975), more than 20 models similar have been generated in nonhuman primates, dogs, rodents and poultry, among which nonhuman primates models are rarely studied, while rodent models are very popular (Narayanan and Chattarji, 2010; Seligman et al., 1975; Willner and Belzung, 2015; Zou et al., 2017).

2.1. Physical induction

2.1.1. Electrical stimulation induction (ESI)

The ESI model is also known as the learned helplessness (LH) model. In the original form, an experimental dog was placed in a closed cage and received repeated electrical stimulation to the point of behavioral despair(Seligman et al., 1975). After that, the cage was opened, and the dog was stimulated with current again. Finally, the dog would show no desire to escape, and it would display symptoms such as decreased appetite, inactivity and weight loss. Today, this form of the ESI model has been replaced by foot shock in rodents (Li et al., 2011; Yan et al., 2018b). Normally, a non-depressed rodent is placed in a cage with an electrified floor, and it will escape immediately or within 5 s. If the animal has a delayed escape latency of 10–19 s or even 20 to 30 s, modeling of depression will be recognized as successful(Wang et al., 2017a). The ESI model simulates the general depressive symptoms of human beings, but the depressive period is short, and most animals recover in a few days (Li et al., 2011). Therefore, the ESI model is not suitable for long-term studies of depression (Li et al., 2011).

2.1.2. Environmental induction (EI)

The EI model can be induced by mild or intense stimulation, either of which causes behavioral despair (BD) in rodents in a short period of time, also called BD test (BDT). Mild stimulation is also called chronic unpredictable mild stress (CUMS), while intense stimulation includes the forced swimming test (FST) and tail suspension test (TST).

The CUMS model was first proposed by Kate and coauthors. (Katz and Sibel, 1982). It has been gradually developed to include more than 10 kinds of stimulation methods. CUMS is generally divided into two categories according to the properties of the stimuli (Fifel et al., 2018; Liu et al., 2018b; Niu et al., 2015): body stimuli (including food and water deprivation, swimming in water at 45 °C or 4 °C, aversive odors, tail pinches and foot shocks) and ambient stimuli (including overnight illumination, wet sawdust or no bedding at all in the cage, tilting the cage 45°, and applying noise stimuli). The above stimuli are administered in random order, one or two daily. Depression-like behavior in rats can usually be induced by 3 to 5 weeks of stimulation (Liu et al., 2018b; Niu et al., 2015; Yan et al., 2018b). When combined with isolation, CUMS shortens the necessary isolation time and prolongs the depressive period in rodents (Wang et al., 2009), generating what is currently considered a classic depression model. It is commonly used for studying the pathophysiological mechanisms of depression as well as screening antidepressants (Liu et al., 2018b; Niu et al., 2015; Wang et al., 2009). The disadvantages of CUMS modeling are the long preconditioning time, the large workload, the unstable results, and the need to eliminate some samples after the experimental induction.

The animals in the BD model are subjected to greater stimulus intensity than those in the CUMS model. The FST was first proposed by Porsolt (Porsolt et al., 1977). Briefly, the rat is placed in a pool with limited space to induce a sense of crisis and despair. When the rat loses hope of escaping, it will no longer struggle. The total durations of swimming, climbing and immobility time are recorded (Porsolt et al., 1977; Shapiro et al., 2019). Another model of BD is the TST (Palucha-Poniewiera et al., 2017), in which a mouse is hung upside down by the tail at a certain height. Usually, the mouse struggles and moves in the beginning; the immobility time will be recorded when it stops. Because the mouse cannot escape, BD is produced. The advantage of the BD model is that it produces depression-like behavior in a short time (Palucha-Poniewiera et al., 2017; Porsolt et al., 1977). However, the reasons for immobility in this model are complicated, and the results may be influenced by some irrelevant factors, such as exercise fatigue and state adaptation, decreasing the face validity of the BD model (Niu et al., 2015).

Table 1
Representative models of poststroke depression.

Authors	Model	Assessment methods	Results	Advantages[a]	Disadvantages[a]
Kato et al., (2000)	MCAO	Shuttle-box test	Escape failure in model rats (day 15);attenuated by T-794	None	Short duration
Verma et al., (2014)	MCAO + isolation	SPT, TST and social interaction test	Increased immobility, reduced sucrose consumption and social contact behavior; reduced arginase-1 and increased IL-6 expression, and brain atrophy after 6 weeks	No direct induction, little time required	Needs further research to confirm
Karelina et al., (2009)	Isolation + MCAO	OFT and paw preference test	Increases in infarct size, edema, and mortality in isolated mice; down-regulated of IL-6 in brain, up-regulated of peripheral IL-6 72 h after MCAO	Suitable model for patients living alone and later having a stroke	High mortality
Niu et al., (2015)	MCAO + isolation + CUMS	SPT, OFT and body weight test	Reduced bodyweight, sucrose consumption ratio, spontaneous movement and number of rearing events after 8 weeks	Suitable model for acquired environmental stress after stroke	Time-consuming model generation
Balkaya et al., (2011)	Chronic stress + MCAO	TST	Increased ischemic lesion size and superoxide production; reduced brain endothelial nitric oxide synthase levels; reversed by mifepristone 72 h after stroke	Suitable model for patients who have a history of depression and then develop stroke	Time-consuming model generation; high mortality
Zhang et al., (2015)	MCAO + spatial restraint	FST, TST, SPT, grip- traction test and foot- fault test	60 min of ischemia is the best choice, accompanied with reduced levels of BDNF, serotonin and dopamine; reversed by impramine for 2 weeks; 70 min leads to major depression and aggravated mortality	Suitable model for patients with severe spatial restrictions on their activity	Limitation is imposed by the external environment
Aggarwal et al., (2010)	Bilateral common carotid artery ischemia reperfusion	FST, locomotor activity and inclined beam-walking test	Increased immobility period, neurological scores and oxidative stress markers, and decreased locomotor activity after 96 h of reperfusion; reversed by treatment of naringin	No induction; suitable model of acute depression after stroke	Short duration (4 days)
Caso et al., (2008)	Restraint stress + electrocoagulation of MCA	Body posture, spontaneous activity, gait and touch escape test	significantly slackened body posture, reduced spontaneous activity, and diminished touch escape behavior after 7 days; accompanied by inflammatory response and lipid peroxidation	TLR-4 as anew treatment target for PSD	Prone to infection
Kozlowski et al., (1996)	Heat-induced cortex lesions + restraint	Forelimb placing test; limb-use observations	Obvious behavioral dysfunction, severe neuronal injury; prevention of dendritic growth in the restricted unimpaired forelimb after 15 days	Lesion limited to the cortex	Prone to infection; high mortality
Pan et al., (2014)	Heat-induced cortex lesions + CUMS	SPT	22 major differentially expressed proteins were found in ipsilateral hippocampus after 3 weeks; Grp75, peroxiredoxin-6 and prohibition involved in PSD induced injury	Lesion limited to the cortex	Prone to infection; high mortality
Vahid-Ansari et al., (2016)	Prefrontal injection of endothelin-1	OFT, TST, FST, NSFT, elevated plus maze, horizontal ladder test	Typical depression- and anxiety-like behavior after 6 weeks, accurate lesion in the left mPFC; no motor or sensory abnormalities	No induction; no rodents died; suitable for silent stroke	Needs further research to confirm
Nemeth et al., (2012)	Internal carotid arterial injection of microembolism	SPT, OFT, SIT and Barnes maze test	Delayed anxiety- and depression-like behavior (day 14 to 17); spatial memory impairment on the 33rd day	No induction; no significant neurological deficits; vascular depression	Poor reproducibility of lesions
Jin et al., (2017)	Photochemical cortical lesion + isolation	SPT, FST and body weight measurement	Increased immobility time and decreased sucrose consumption, reversed and up-regulated of BDNF by 14 days of treatment with fluoxetine	Investigators can freely select the cortical area of interest; low infection and high survival rate	Time-consuming induction

[a] Representing the points we discuss in this review. PSD: poststroke depression; MCAO: middle cerebral artery occlusion; MCA: middle cerebral artery; BDNF: brain-derived nerve growth factor CUMS: chronic unpredictable mild stress; SPT: sucrose preference test; OFT: open field test; TST: tail suspension test; FST: forced swimming test; SIT: social interaction test; NSFT: novelty-suppressed feeding test; mPFC: medial prefrontal cortex; TLR-4: Toll-like receptor 4.

2.2. Chemical induction (CI)

CI is also known as drug induction. Reserpine is widely used to inhibit central nervous function by depleting the synaptic cleft of dopamine and serotonin (Zhang et al., 2018b). This manipulation induces signs of depression such as decreasing body temperature, drooping eyelids and inactivity. This model is easy to generate, and it can be reversed by antidepressant treatment, but it lacks selectivity and is prone to false positive antidepressant effects. In addition, withdrawal of 5-hydroxytryptamine (5-HT), yohimbine, apomorphine, corticosterone and some psychostimulantsmay induce depression-like behavior (Kinze, 2015; Zhang et al., 2018b). However, these models have low credibility and poor construct validity, differing significantly from human depression. Therefore, CI models can be used only as preliminary screening assays for antidepressants (Kinze, 2015; Li et al., 2016b).

2.3. Social stress induction (SSI)

SSI models have similar characteristics to human social life. At present, there are two methods for SSI: one in which a weaker animal is attacked by a stronger animal(Wang et al., 2017a), and one based on maternal separation (Nishi et al., 2014). Social conflict is inevitable for all animals as they compete with each other for survival. When a male rat is placed in a cage that is already inhabited by a family group of rats, the new comer is considered an intruder and will be attacked and threatened by the original male rats. Repeated physical and mental stress stimuli can induce depression-like behaviors such as anhedonia, reduced activity, insomnia, and altered appetite in invading rats, with or without manifestations of anxiety(Wang et al., 2017a). The advantage of SSI is that it simulates the properties of human social stress, but this model takes an undesirably long time to generate.

The maternal separation model has its most pronounced effects when applied very early in life (Mooney-Leber and Brummelte, 2017; Nishi et al., 2014; Wei et al., 2018). In this model, rodent pups are raised apart from their mother; they are deprived of their maternal bond. The lack of maternal attachment can induce dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in the pups (Jafari et al., 2018; Mooney-Leber and Brummelte, 2017). Due to changes in neurotransmitter levels and endocrine parameters, young rodents readily produces behavioral abnormalities that persist in adulthood, and the sensitivity of treated animals to CUMS induction is also significantly higher than that of other rodents (Wei et al., 2018). This model, which simulates the social stress of human infants who lack maternal love, is useful for studying the etiological mechanism of adulthood depression in individuals who experience early social stress during growth.

2.4. Surgical induction (SI)

The olfactory bulb is associated with the limbic system. Surgical removal of the bilateral olfactory bulbs reduces the passive avoidance response and increases plasma steroid levels, resulting in depression-like behaviors such as anhedonia, impairment of spatial learning and memory, and decreased appetite and libido (Babinska and Ruda-Kucerova, 2017; Lessard-Beaudoin et al., 2019). The SI model has face validity and construct validity, but the procedure is difficult, with a high mortality rate because of infection (Babinska and Ruda-Kucerova, 2017; Lessard-Beaudoin et al., 2019; Li et al., 2015).

2.5. Genetic induction (GI)

Hereditary depression is usually related to genetic mutation or inbreeding. At present, there are several models that simulate human depression-like symptoms to varying degrees: the Flinders Sensitive and Resistant Line (Hesselberg et al., 2016; Thiele et al., 2018), Wistar Kyoto (Hurley et al., 2013) and Fawn-Hooded rat models (Knapp et al., 2018). In addition, transgenic or conditional gene knockout of neurotransmitters, receptors, and transporters has been applied to generate mouse depression models, which showed good construct validity (Gertz et al., 2018; Hesselberg et al., 2016; Hurley et al., 2013; Jin et al., 2017; Knapp et al., 2018; Lim et al., 2018). However, GI models are expensive, and the mechanism of depression is very complex; therefore, the practical applications of GI are limited.

3. 2. PSD models

Human PSD is more complicated than general depression. PSD models are always unsatisfactory due to their multiple etiological features (Kronenberg et al., 2014). Currently, it is most common to use a composite model because of its collective characteristics. Specifically, cerebral ischemia is first induced, and depression is then superimposed. This model has strong face validity and is considered a type of PSD model (Robinson and Jorge, 2016; Wang et al., 2017a), but its construct validity is poor. In addition to models with neurological deficits, models of depression-like behavior with silent stroke and vascular depression have also been reported recently (Kronenberg et al., 2014; Nemeth et al., 2012; Vahid-Ansari et al., 2016). A simplified description of PSD models is given in Table 1.

3.1. Middle cerebral artery occlusion (MCAO) model

In 2000, based on Nagasawa's protocol (Nagasawa and Kogure, 1989), Kato et al. (2000) conducted an MCAO model for SD rats. The middle cerebral artery is occluded for 2 h and then reopened. Neurological examination was performed on the 1st and 7th days after surgery according to the method of Barone (Barone et al., 1995). Behavioral function was assessed with a two-way shuttle box test. It was found that the monoamine oxidase inhibitor T-794 not only reduced the rats' failure rate in the shuttle box test but also increased the levels of dopamine, norepinephrine and 5-HT in the affected cerebral hemisphere (Kato et al., 2000). The activity levels of almost all rats were decreased in the early stage after cerebral ischemia (Lin et al., 2018; Tao et al., 2015), and these changes were associated with central inhibition and impairment of sensorimotor functions, whereas the animals did not show any core symptoms of clinical depression, such as lack of interest and reduced social activity(Kato et al., 2000). Frequently used behavioral evaluations include the Sucrose Preference Test (SPT) and FST (Cheng et al., 2013; Kronenberg et al., 2012), which can be used to evaluate the core symptoms of depression. However, for the MCAO models have a common shortcoming: the duration of depression is short, and some of the rodents display anxiety-like behavior (Boyko et al., 2013; Kronenberg et al., 2012). In addition, the face and construct validity are seriously deficient, and some studies have reported that depression-like behavior can be reversed by citalopram due to the increase in brain-derived nerve growth factor in the infarcted side(Espinera et al., 2013), but further studies on related neurotransmitters and receptors are lacking. Therefore, the simple MCAO model is not an ideal PSD model.

3.2. “MCAO + isolation” model

In one model used to verify the effects of social isolation on cerebral ischemia, young male mice are housed in pairs for 14 days before induction of MCAO(Verma et al., 2014). The tissue was reperfused after 60 min of MCAO on the right side. The mice were divided into isolated and paired groups. The SPT, the TST and the social interaction/sociability test were performed weekly for 6 weeks. The results showed that isolation not only increased the duration of immobility in the TST and reduced sucrose consumption in the SPT but also decreased social contact behavior. Furthermore, the isolated mice group displayed obvious brain atrophy, and the expression of arginase-1 around the infarct was significantly increased. Therefore, the “MCAO + isolation” model has both face validity and construct validity. Alternatively, the treatments can be applied in the opposite order, generating the "isolation+ MCAO" model, which increases infarct size more significantly (Balkaya et al., 2011; Karelina et al., 2009; Venna et al., 2012), without any behavioral changes of depression.

3.3. "MCAO + isolation+ CUMS" model

This model is a typical dual modeling method for cerebral ischemia with superimposed depression, which is currently the most widely used PSD model(Chen et al., 2015; Niu et al., 2015; Wang et al., 2008b; Wang et al., 2009). It was first proposed by Belayev (Belayev et al., 1996) and has been studied and improved since then. Briefly, the middle cerebral artery of a rat or mouse is embolized on one side to cause permanent cerebral ischemia (Ran et al., 2018; Yan et al., 2018a; Zhang et al., 2018a). The animal is singly housed after surgery, and its neurological function score is measured. CUMS induction is started 3 or 7 days after surgery, and 7 to 12 specific types of stimulation are used (Niu et al., 2015; Wang et al., 2009). Typical depression-like behavior occurs within 2 to 3 weeks, although some applications require 5 weeks or even longer depending on the purpose(Chen et al., 2015; Wang et al., 2008b). The success of the model induction can be verified by the SPT, the FST or the open field test (OFT). Depression-like behaviors and reduced proliferation of neurons in the dentate gyrus can be reversed by citalopram administration (Wang et al., 2008b). In addition, Niu(Niu et al., 2015) adopted a method of transient cerebral ischemia, with 2 h of occlusion followed by reperfusion. CUMS was induced with a mild stimulus randomly selected among 12 options. In this model, animals lost their typical interests within 8 weeks after stroke (Niu et al., 2015).

From the available data, the combined model has strong face validity, but its construct and predictive validity are still insufficient. This model is fundamentally different from clinical PSD. Although PSD patients are influenced by exogenous environmental factors, the endogenous pathophysiological changes are the most common and fundamental reason for depression (Meng et al., 2017; Robinson and Jorge, 2016; Villa et al., 2018). Therefore, this model is good for basic research on depression caused by acquired environmental stress after cerebral infarction.

The treatments can also be applied in the opposite order to generate the "CUMS + MCAO" model, which increases the volume of the cerebral infarct compared with the simple MCAO model (Custodis et al., 2011; Kronenberg et al., 2014). However, the reason why this model has different effects than the "MCAO + CUMS" model remains unknown. The "CUMS + MCAO" model mimics clinical patients who have a history of depression before suffering from cerebral infarction. The increased infarction in this model suggests that depression aggravates ischemic cerebral infarction, which is of great significance.

3.4. Bilateral common carotid artery ischemia-reperfusion model

Using a modified version of the method described by Kelly and coworkers (Kelly et al., 2001), Aggarwal generated an ischemic mouse model. The arterial sheath and vagus nerve were separated under anesthesia, and ischemia was induced by occluding the bilateral common carotid arteries with clamps in two 5-min bouts 10 min apart (Aggarwal et al., 2010; Daglia et al., 2017; Gaur and Kumar, 2010). The mice were monitored during the operation to verify the maintenance of dilated pupils and the absence of a corneal reflex on exposure to strong light stimulation. An inclined beam-walking test was performed to assess forelimb and hindlimb motor coordination after 96 h (Feeney et al., 1981). The FST showed that the immobility period and latency were significantly prolonged (Aggarwal et al., 2010). There was no superimposed induction program during the operation; in this respect, the model is similar to clinical PSD. Furthermore, the brain tissue showed an increase in oxidative stress markers (Aggarwal et al., 2010). This model has a certain degree of face validity and construct validity. However, the author observed the animals for only 4 days after stroke, examining only acute rather than chronic depression after cerebral ischemia(Aggarwal et al., 2010; Gaur and Kumar, 2010); furthermore, the authors used only the FST to assess depression, suggesting that the validity of the evaluation was insufficient. Later, this model was used by Nabavi to study PSD (Nabavi et al., 2016). The SPT and the TST were added to assess depression, but the observation period was only 1 week (Nabavi et al., 2016). Long-term observation is lacking in both studies (Aggarwal et al., 2010; Nabavi et al., 2016). Finally, it has also been confirmed that rapid eye movement latency is shortened in the bilateral common carotid artery ligation model of PSD(Wang and Song, 2010).

3.5. "Restraint stress + electrocoagulation of middle cerebral artery (MCA)" model

In the original iteration of this model, mice were subjected to spatial restraint stress in a ventilated tube, and an opening in the end of the container for the tail of the mouse (Caso et al., 2008). The mouse was not able to rotate or to move forward or backward in this tube. Repeated restraint was applied between 10 am and 11 am daily for 7 days. Then, focal cerebral ischemia was induced by permanently occluding the MCA using electrocoagulation 24 h after the last immobilization exposure. Briefly, the mice were anesthetized with 5% isoflurane for induction and 1.5% isoflurane for maintenance. An incision was made perpendicular to the line connecting the lateral canthus of the left eye and the external auditory canal to allow the temporalis muscle to be exposed and retracted under a microscope. A burr hole was drilled in the skull, and the MCA was exposed by cutting and retracting the dura mater. The MCA was elevated and cauterized with an electrocoagulator. Then, the incision was closed, and the mouse was returned to the original cage with free access to water and food. Behavioral tests showed that the model group had significantly slackened body posture, reduced spontaneous activity, slowed gait, and diminished touch escape behavior compared with the control group (Caso et al., 2008). From the perspective of the modeling process, it conforms to certain characteristics of PSD, but the stress protocol is very simple, and the subsequent behavioral assessment also lacks the core content of depressive symptoms. Inflammatory response and lipid peroxidation associated with stress were detected (Caso et al., 2008), but no other depression related markers were identified. The opposite operating procedure "electrocoagulation plus isolated" was also reported in aged and young rats (Buchhold et al., 2007). Aged rats showed more serious behavioral damage compared to young rats (Buchhold et al., 2007), but characteristically assessing (such as SPT) of depressive behavior was also absence in this report. Further study is needed to determine whether this model is suitable for research on PSD.

3.6. "MCAO + spatial restraint" model

This model was developed by Xu's research team in 2015, which applied the MCAO model followed by spatial restraint stress (Zhang et al., 2015). Briefly, MCA embolization and spatial restraint were performed as described for the "MCAO"(Kato et al., 2000) and "restraint stress + electrocoagulation of MCA"(Caso et al., 2008) models above. The difference between this model and the others is the timeline. In fact, the surgical process is no different from that of previous MCAO models except in terms of ischemia time (50 min, 60 min and 70 min). On the fourth day after MCAO, mice were placed into a modified, well-ventilated 50-ml centrifuge tube from 9 am to 11 am daily for 2 weeks. After restraint stress, the mice were removed from the tube and returned to their original cages. In addition to tests of depressive behavioral, including the FST, TST and SPT, modified grip-traction tests, foot-fault tests and body weight measurements were also performed weekly after MCAO to evaluate the effects of induction of PSD. PSD-like depressive phenotypes were reliably detected in 60-min MCAO mice, accompanied by reduced levels of brain-derived neurotrophic factor, serotonin and dopamine. All the observed markers could be reversed by the administration of imipramine (Zhang et al., 2015). The advantage of this model is that it determines the importance of ischemic time (60 min) for PSD induction; 70 min of cerebral ischemia led to major depression, which increased mortality, and 50 min was less effective at inducing symptoms.

This model is a good example of all three types of validity, but two questions remain as following. From the figure in the results section of the article, the survival rate of the 70 min ischemic group (less than 30%) was significantly lower than that of the 60 min ischemic group (visually estimated at 70–80%) on day 7 (Zhang et al., 2015). Why did a 10-min difference in ischemia time lead to a significant difference in survival? The authors did not clearly explain the reasons. One possible interpretation, according to our analysis, is that the restraint stress was performed at the peak of cerebral edema (3–4 days after MCAO), which may aggravate brain edema after reperfusion and lead to death. However, in previous MCAO models, ischemia time very commonly ranges from 60 min to 120 min (Bouet et al., 2007; Cheng et al., 2013; Verma et al., 2014; Wu et al., 2018) or even permanent ischemia (Boyko et al., 2013), and such high mortality has not been reported in the literature. Does spatial restraint stress truly aggravate rodents' cerebral edema and infarction? Just as in the “CUMS + MCAO” model, described in “MCAO + isolation + CUMS” (Custodis et al., 2011; Kronenberg et al., 2014), spatial restraint could increase the size of an infarction. More research is needed to support these possibilities, especially whether and how restraint stress itself causes general depression. If the peak period of cerebral edema is not suitable for the application of restraint stress, the start of stress induction should be delayed.

3.7. “Heat-induced cortex lesions + restraint or CUMS” model

The operation process of this model is slightly different from that of the “restraint stress + electrocoagulation of MCA” model (Caso et al., 2008) described above. The rats are anesthetized, followed by atropine sulfate to facilitate respiration (Kozlowski et al., 1996). A unilateral lesion to the forelimb representation area of the sensorimotor cortex is produced a stereotaxic apparatus. A piece of the skull between 3.0 and 4.5 mm lateral to the midline, and between 0.5 mm posterior and 1.5 mm anterior to bregma is removed. A current of 1 mA is delivered to the exposed cortex for 2 min at equal intervals through a platinum electrode inserted 1.7 mm below the dura. Casts are used to restrict forelimb movement and removed 15 days after surgery. Interestingly, restricting the unimpaired forelimb resulted in obvious behavioral dysfunction (as detected, for example, by limb-use observation and the forelimb placing test) 2 days after the cast was removed, but no such effect occurred when the impaired forelimb or neither forelimb was immobilized. In addition, immobilization of the unimpaired forelimb led to prevention of layer V pyramidal cell dendrite growth in the intact contralateral homotopic cortex and severe neuronal injury in the lesioned hemisphere.

This is another case in which “stroke plus restraint stress” can aggravate brain damage. Although the researchers did not use the typical methodology to assess depressive behavior, the overall modeling process and postoperative behavioral characteristics of the rats were very consistent with the characteristics of PSD.

Later, Pen and coauthors (Pan et al., 2014) improved the modeling methods on this basis. Producing heat-induced cortical lesions first and then adding CUMS induction for 3 weeks could also generate a typical PSD model. Proteomic analysis of the ipsilateral hippocampus showed that 22 differentially expressed proteins involved in cytoskeletal remodeling, neurogenesis and energy metabolism were regulated in opposing directions by stroke and PSD (Pan et al., 2014). In contrast to MCAO, the heat-induced cortical lesion model mainly damages the cerebral cortex, while the subcortical structure is not involved or very little. Therefore, this model has the advantage of directionally inducing cortical damage during surgery, but it has several disadvantages in that the procedure to establish the model is complicated, the rodents are prone to intracranial infection, and the mortality rate is high (Kozlowski et al., 1996).

3.8. “Prefrontal injection of endothelin-1 (ET-1)” model

This highly innovative model was reported by Vahid-Ansari in 2016 (Vahid-Ansari et al., 2016). Male C57BL/6 mice were selected and housed in pairs under standard conditions for 2 weeks before surgery. The specific modeling process was as follows: mice were anesthetized with 5% isoflurane for induction and 1.5 to 2% isoflurane for maintenance prior to stereotaxic surgery. ET-1 was suspended in sterile water (2 μg/μl) and sonicated at 4 °C for 15–20 min. Then, 1.0 μl was pumped into the target brain tissue at a rate of 0.2 μl/ min using a micro injector. Two sites in the left medial prefrontal cortex (mPFC) at the coordinates relative to Bregma were selected. The needle was left in place for 3 min after the end of the injection. After the operation, the mice were placed in a 37 °C incubator until they resumed physical activity. The pain was relieved by buprenorphine 3 h after surgery, and the mice were returned to their home cage for feeding.

Behavioral assessments such as the OFT, the TST, the FST, the novelty-suppressed feeding test (NSFT), observation of circadian rhythms, and the elevated plus maze were performed after stroke (Vahid-Ansari et al., 2016). Model mice displayed typical depression and/or anxiety-like behavior after 6 weeks. Cresyl violet staining showed accurately placed lesions in the left mPFC including the cingulate gyrus and the prelimbic and infralimbic areas. Detailed analysis of the staining further demonstrated that there was very little variability between mice. In addition, magnetic resonance imaging (MRI) showed mPFC infarcts in vivo that were consistent with the ones revealed by postmortem staining. However, the horizontal ladder test and the cylinder test indicated that these mice had no sensorimotor abnormalities, an outcome consistent with the characteristics of “silent stroke” (Faraji et al., 2012).

Compared with previous brain embolism models or global cerebral ischemia models, this model has great advantages. First, the characteristics of the lesions are consistent with the classic brain circuit theory of “lesion to depressive behavior” (Hu et al., 2008; McCoy et al., 2016; Ruggiero et al., 2018; Thiele et al., 2018). Second, the low interest and anhedonia in model rodents are due to the direct effects of PSD but not the indirect effect of abnormalities in motor function (Vahid-Ansari et al., 2016). Third, the ET-1-induced lesions are very small, precise and reproducible, and no rodent deaths were reported (Vahid-Ansari et al., 2016). The methodology of this model is worth learning and promoting. We can attempt to form ischemic foci in different lobes or subcortical structures of the brain to study the relationship between specific lesions and PSD. Studies of molecular markers and antidepressant interventions would be useful for the evaluation of validity.

3.9. “Internal carotid artery microembolism” model

Adult male Wistar rats aged 3 months were housed in pairs in a standard environment to adapt to their environment before surgery (Nemeth et al., 2012). The rats were anesthetized with isoflurane, and the common carotid artery was carefully separated, isolated and ligated, after which the external carotid artery was ligated at the bifurcation of the artery. Microspheres measuring 50 μm in diameter were injected into the internal carotid artery with a 30G needle to generate micro-embolic lesions. The injection site was pressurized, and the silk thread was released to restore blood flow. The SPT, the OFT and the social interaction test (SIT) were evaluated at either a short-recovery (SR) time point (4–6 days after surgery) or a long-recovery (LR) time point (14–17 days after surgery). The results showed that rats with microembolic infarcts displayed an increase in anxiety-and depressive-like behaviors at the LR point but not the SR point, suggesting that microemboli induced a delayed increase in those behaviors. In addition, the Barnes maze test showed obvious spatial memory impairment in rats with microembolic infarctions on the 33rd day after stroke. In contrast to the MCAO model, this model features very small lesions and no significant neurological deficits. However, the microembolism damage is diffuse and variable among LR rats, with 25% of rats showing midline shifting and 31.3% showing asymmetrical cystic space-occupying lesions greater than 300 μM in diameter in the amygdala, caudate, cortex, hippocampus and hypothalamus. Interestingly, the quantification of damage revealed no predictable relationship between lesion volume and behavior, indicating that alterations in neuronal function may underlie behavioral deficits (Nemeth et al., 2012). Therefore, this model is consistent with the dysfunction caused by extensive small vessel disease and could be used as a model of vascular depression(Taylor et al., 2013). However, further research is needed on its construct and predictive validity.

3.10. "Photochemical cortical lesion + isolation" model

In 1977, Rosenblum and El-Sabban first proposed the concept of photothrombosis (Rosenblum and El-Sabban, 1977). Later, Watson et al. applied it to the rat brain and set the basis of the current photothrombotic stroke model (Watson et al., 1985). Briefly, a light-sensitive dye is injected intraperitoneally and enters the circulatory system of the rat. The dye is activated by illumination and produces singlet oxygen, which damages the components of endothelial membranes, resulting in platelet aggregation, thrombosis and local blood flow interruption in the areas of interest exposed to light (Labat-gest and Tomasi, 2013; Watson et al., 1985). A minimally invasive and reproducible mouse model of stroke based on photochemical cortical lesions was further introduced and studied by Labat (Labat-gest and Tomasi, 2013). Later, Jin et al. modified the method introduced by Labat and established a PSD mouse model by employing ischemia in the left anterior cortical layers through photothrombosis and housing the mice in isolation (Jin et al., 2017). Briefly, mice were anesthetized with chloral hydrate. The scalp was incised, and an optic fiber illuminating a cold light source was positioned against the left surface of the skull. The photosensitive dye rose bengal was administered intraperitoneally, and focal illumination was applied to the skull for 15 min, starting 5 min after the dye was administered. Then, the incisions were sutured, and the animals were singly housed for 2 months. Before stroke modeling and after 2 months of social isolation, the SPT, the FST and body weight measurement were performed on separate occasions. The results showed that immobility time was increased and sucrose consumption was decreased in experimental mice; 14 days of fluoxetine administration reversed this pattern and was accompanied by up regulated Brain-derived nerve growth factor (BDNF) expression in the hippocampus (Jin et al., 2017).

This model is significantly different from the previous model. In the process of modeling, the light source can be applied to the intact skull with no craniotomy, allowing ischemic damage to be induced in an area of interest in a noninvasive way. Therefore, the internal brain tissue is not in direct contact with any substance in the outside world, and the probability of an infection or rejection reaction (suture for MCAO) is extremely low; accordingly, the survival rate of this model is reported to be very high(Jin et al., 2017). From the 2,3,5-triphenyltetrazolium chloride (TTC) staining and MRI images provided by the authors, it can be seen that the cerebral infarction lesions are limited mainly to the cerebral cortex, which is a reproducible outcome as reported in the previous study (Hu et al., 2008; Labat-gest and Tomasi, 2013; Taylor et al., 2013; Watson et al., 1985). Therefore, according to different requirements, cold light irradiation can be used to induce precise lesions in different cerebral cortical areas of interest, thus facilitating research on the "brain circuit theory" of PSD. In addition, precise cell characterization or functional studies of transgenic mice could be achieved in this noninvasive, craniotomy-free model (Jin et al., 2017; Labat-gest and Tomasi, 2013). The disadvantage, of course, is that the subsequent stress induction is time consuming.

4. Assessment of core symptoms

Assessment of PSD behavior should address the criteria for clinical depressive symptoms, such as anhedonia, low mood, decreased social interaction behavior, and even despair (Hu et al., 2008; Meng et al., 2017; Robinson and Jorge, 2016). At present, there are many methods of behavioral assessment, and some have been improved by scholars. The following is a brief description of the assessment methods that examine the core symptoms of clinical depression.

4.1. SPT

Sucrose intake can bring pleasant emotions to almost all animals. A decline in sucrose consumption ratio reflects animals' reduced or absent sensitivity to rewarding stimuli. The SPT is currently the most appropriate assessment method for core symptoms of depression (Jin et al., 2017; Nemeth et al., 2012; Niu et al., 2015; Pan et al., 2014; Tchekalarova et al., 2018; Verma et al., 2014; Zhang et al., 2015). Generally, it is divided into an adaptation period and an assessment period: first, animals are presented with two bottles of 1–2% (wt/vol.) sucrose solution for the initial day of adaptation, followed by one bottle of tap water and one bottle of sucrose solution for the next day; second, after habituation, the animals are deprived of food and water for 12 h, and the sucrose solution and tap water are reintroduced to the animals during the assessment period. Animals choose freely whether to drink the sucrose solution or the tap water. At the end of the evaluation, the volumes of sucrose solution and tap water consumed by the animals are recorded. The sucrose preference ratio is calculated as [(sucrose consumption)/ (water consumption + sucrose consumption)] × 100. Previous studies have demonstrated thata diversity of stressors, such as CUMS and chronic social defeat, substantially decrease the preference for sucrose solution (Niu et al., 2015; Pan et al., 2014), while administration of antidepressants restores the sucrose preference ratio(Jin et al., 2017; Zhang et al., 2015). This SPT method has been widely used in the past few decades, and few have questioned or criticized it. Recently, some scholars have proposed that it is necessary to re-examine the SPT (Liu et al., 2018a). Because the results of SPT are affected by many factors, such as age, sex, strain, diet, weight, environment, test time, failure to drink the liquids, excessive consumption of the liquids, and differences in the handing of mice, the degree of variability is very high (Bertino and Wehmer, 1981; Liu et al., 2018a; Tordoff and Bachmanov, 2002). A key challenge has been the lack of a standardized and efficient device to use for the bottles. Liu et al. (Liu et al., 2018a) improved the protocol, including an adaptation period (day 1 to day 4), baseline measurement (day 4 to day 6), deprivation (day 6 to day 7) and SPT (day 7 to day 8), in which the definitions of "no drinking" and "over drinking" were identified, relevant exclusion criteria of assessment were established, and a specific apparatus consisting of ten chambers (length 24 cm × width 24 cm × height 13 cm for each) was designed. Later, according to those standard operating procedures, accurate and reasonable sucrose preference ratios were obtained. Their work was published in *Nature Protocols* in July 2018. This procedure established by Liu and coauthor is an effective assessment of anhedonia as a core symptom of depression and is highly recommended by its creators (Liu et al., 2018a). This study addresses the previous lack of fixed standards and test equipment for the SPT and provides a reference for collecting standard results from different rodents.

4.2. NSFT

Exposure of animals to the novel environment has a delay of chewing and suppressive effect on the amount of food consumption. This finding was firstly done by Britton in 1981 and is very useful for evaluating anxiety rodents (Britton and Britton, 1981). Rats were placed in a novel environment, and their anxiety-behavior was assessed by observing the latency to the first bite, total amount of food eaten, the number of approaches to the food pedestal and even the incidence of urination in 15 min (Britton and Britton, 1981). Later, this assessment method was improved to varying degrees and applied to depressed animals (Tchekalarova et al., 2018; Vahid-Ansari et al., 2016). The animals are generally deprived food for 16 or 48 h (Tchekalarova et al., 2018; Vahid-Ansari et al., 2016). After 3-min acclimation or 30-min passive movement, the animals were placed in a novel open field with a food pellet placed in the center. After 10 min of testing, the animals are returned to their home cage. The latency of the animals to begin eating food is recorded, and the amount of food actually consumed is also calculated. If no food is consumed within 5 min, the latency is recorded as 5 min (Vahid-Ansari et al., 2016). Recently, a standardization protocol including three-phase deprivation and the introduction of highly standardized palatable food was proposed by Blasco-Serra (Blasco-Serra et al., 2017). This standardization has been shown to be effective in measuring the effects of antidepressants. Therefore, the introduction of standardized recommendations would reduce interlaboratory variability and improve the effectiveness and robustness of this behavioral test (Blasco-Serra et al., 2017). Although the NSFT is used to assess the behavioral effects of depression and antidepressants, it is also highly sensitive to stress-induced anxiety (Iijima et al., 2012).

4.3. SIT

A dimly lit chamber was prepared (File and Hyde, 1978; Nemeth et al., 2012). The model rat was placed in the center of the box, in which an ovariectomized female rat has been placed in advance. The latency of the model rat to contact the female and the total contact time, including sniffing, biting, grooming, following, mounting, attacking and jumping, is recorded by video. Importantly, only the active contact time of the experimental rats is recorded, while the passive contact time is excluded. The total observation time is 10 min. This process is completed by two raters, whose measurements of total contact duration must be within 10 s of each other. In addition to being used to assess depression, the SIT is also suitable for assessing certain characteristics of anxiety behavior (File and Hyde, 1978; Toth and Neumann, 2013).

4.4. BDT

The BDT contains two methods, namely, the FST (Porsolt et al., 1977; Shapiro et al., 2019) and TST (Palucha-Poniewiera et al., 2017), which have been described in EI. The main outcome of interest is immobility time, which reflects the level of behavioral despair in rodents. The BDT can be used as both the induction method for CUMS and the evaluation method for the effect of the model (Balkaya et al., 2011; Mou et al., 2017). Both of these methods are currently in widespread use. It should be noted that the TST is widely used in to assess behavior in mice but not in rats because it's the larger size of the latter makes them more difficult to control(Wang et al., 2017a).

4.5. OFT

Generally, computer infrared video is used to monitor the activity of animals (Li et al., 2017). The animals are placed in a novel open field arena and allowed to explore the new environment for several minutes (e.g., 10 min). Then, the time and distance traveled in the center and corners, the average moving speed and the proportion of movement in the central area are analyzed. The OFT could be used to assess the motivation of the experimental animals to explore as well as their anxiety levels and physical activity in the new environment (Karelina et al., 2009; Li et al., 2017; Nemeth et al., 2012; Niu et al., 2015; Vahid-Ansari et al., 2016).

4.6. Others

Several maze tests (the Morris water maze, the elevated plus maze and the Barnes maze) are useful for evaluating the spatial exploration capabilities of rats and mice (Luo et al., 2016; Nemeth et al., 2012; Vahid-Ansari et al., 2016). Compared with the FST, maze tests can also reduce the risk of water aspiration (Luo et al., 2016). In addition, the horizontal ladder test, cylinder test, shuttle box test and water spray test capture the physical activity of PSD animals at a certain level (Kato et al., 2000; Shiota et al., 2016; Vahid-Ansari et al., 2016). These methods can also be applied to PSD animals that have concurrent cognitive or motor impairment (Luo et al., 2016; Nemeth et al., 2012).

5. Discussion

The pathophysiology mechanism of PSD is complex and multifactorial, including ischemia-induced neurobiological disorder and psychosocial distress. In addition to psychological factors, a large number of neurobiological factors were found to be involved in PSD (Villa et al., 2018). 1) Monoaminergic hypothesis. The reduced levels of 5-HT, dopamine and norepinephrine were widely recognized in prefrontal lobe, temporal lobe and limbic system of ischemic models (Ji et al., 2014; Wang et al., 2010; Zhang et al., 2015). Particularly, the upregulated expression of 5-HT receptor 2B mRNA and protein was found in the peri-infarcted (cortical) area of aged rats and stroke patients with depression, which further supported the role of monoaminergic hypothesis in PSD (Buga et al., 2016). 2) Glutamate-mediated excitotoxicity hypothesis. With the higher glutamate/creatine ratio in the frontal lobe detected by magnetic resonance spectroscopy in patients with PSD, it was found that plasma glutamate levels at admission were strongly correlated with the development of PSD after 3 months (Cheng et al., 2014; Geng et al., 2017). 3) Inflammatory response theory. Various inflammatory biomarkers and cytokines, including IL-1β, IL-8, TNF-α, IFN-α, Leptin and macrophage migration inhibitory factor have been found to be elevated in the plasma of PSD patients , indicating that inflammatory response may play an important role in the onset and progression of PSD, (Leyton-Jaimes et al., 2018; Wen et al., 2018). Furthermore, intensive studies demonstrated that perfusion deficits in the elderly can activate perivascular and parenchymal microglia and astrocyte, which may contribute to neuroinflammatory responses (Hossain et al., 2018; Li et al., 2019b; Popa-Wagner et al., 2014; Tu et al., 2019; Yang et al., 2018). 4) Vascular depression hypothesis. Vascular factors, such as lacunar infarct and white matter hyperintensities in CSVD, could interrupt monoaminergic transmission from midbrain to brainstem (Taylor et al., 2013). The burden of CSVD is associated with PSD in patients with acute lacunar infarction (Xu et al., 2019; Zhang et al., 2017). This may be related to the loss of tight junction protein Cldn5 that could alter blood-brain-barrier (BBB) integrity and promote IL-6 passage through the BBB and depression (Menard et al., 2017). In addition, both of homocysteine (Hcy) and cystatin C (Cys C) are common plasma metabolites in patients with stroke, and is closely relevant to cerebrovascular injury. Elevated serum levels of Hcy is a predictor of depression after 1 year of stroke onset (Cheng et al., 2018; Zou et al., 2018), while serum Cys C is independent of inflammation associated with depression in PSP and healthy elders (Minev et al., 2010; Weng et al., 2018; Zou et al., 2017). However, the relationship between Hcy and Cys C is unclear and its role in the mechanism of PSD needs further study. 5) Mitochondrial disfunction. Mitochondria is a well-known vital intracellular organelle in energy metabolism. The high demands of energy make the brain extremely sensitive to the loss of blood flow after stroke, as the oxygen, glucose and other substrates mainly supply from the blood (Song et al., 2014). Furthermore, mitochondrial dysfunction may lead to generation of reactive oxygen species, which also play crucial role in the pathophysiology of PSD, Previous study found that the translocator protein and mitophagy related proteins, such as Pink 1 and Beclin 1, were decreased in learned helplessness mice, which further support the mitochondrial dysfunctions in the pathogenesis of depression (Li et al., 2016a). 6) Neurotrophic theory. Lower serum BDNF at admission was independently associated with depression after 3 months in stroke patients (Vogel et al., 2018). Yet, decreased levels of BDNF in depressed rats could be reversed by anti-depressant treatment (Jin et al., 2017; Zhang et al., 2015). Besides, the nutritional supply of neurons is affected by angiogenesis. Activated Notch 1 signaling cascade in the hippocampus, an important regulator of angiogenesis, is associated with the improvement of PSD in rats (Ren et al., 2018). 7) Aging. Unlike the above hypothesis at the molecular, subcellular and cellular levels, aging is a complex physiological and pathological phenomenon that participates multiple levels. Aged rats and humans are more likely to suffer from depression (Buga et al., 2016; Popa-Wagner et al., 2014). The theory of microcirculatory impairment only supports the susceptibility of elderly stroke patients to depression from one point of view, while the study of aging-related genes changes (such as telomere length) may be more meaningful (Buga et al., 2016; Jain et al., 2019; Jin, 2019; Popa-Wagner et al., 2014; Sarkar et al., 2019; Shetty et al., 2019; Song et al., 2019; Wium-Andersen et al., 2017). 8) Abnormalities of HPA axis and immune response and even damage of prefrontal-subcortical circuits were also widely reported (Shao et al., 2019). However, a pathophysiological hypothesis of PSD that can integrate these theories into a coherent explanatory model has yet to be formulated.

Constructing a reasonable model is vital for studying of pathophysiological mechanisms of PSD. Depression and stroke interact with each other: stroke increases the risk of depression, and depression is an independent risk factor for stroke or recurrent stroke (Robinson and Jorge, 2016; Sibolt et al., 2013; Villa et al., 2018). At present, knowledge about the etiology and pathophysiological mechanisms of PSD is still limited. There are some limitations to the existing PSD models because they are based on one aspect of its clinical features; they cannot simulate complex environmental factors, such as academic qualifications, economic status, family relationships, and social support (Meng et al., 2017; Robinson and Jorge, 2016; Villa et al., 2018). Among the 10 PSD models mentioned above, “prefrontal injection of endothelin-1” and “photochemical cortical lesion + isolation” models have great potential value for the study of the brain circuit theory of PSD (Jin et al., 2017; Vahid-Ansari et al., 2016). Although the “internal carotid artery microembolism” model can simulate vascular depression well, the location of infarct lesions is scattered and uncertain (Nemeth et al., 2012). The unsatisfactory reproducibility of this model may limit the scope of its application. Extensive work is needed to build models for MCAO and stress and optimize the timing of stress induction. In addition, we can build PSD models based on depression-related gene mutations and superimpose them on stroke to study the role of related genotypes in the development of PSD and explore possible treatments.

PSD is a common disease, and the relationship between stroke and depression is not limited to the sequence of events (earlier and later) or causality (cause and effect). PSD varies from case to case just as primary depression does. Although PSD models cannot perfectly replicate the characteristics of every case, there are always opportunities to innovate modeling methods, especially in nonhuman primates.

In the process of human PSD diagnosis, questionnaires are very important (Meng et al., 2017; Robinson and Jorge, 2016), but this method is not applicable animal models. Anhedonia, low mood and reduced activity are the main symptoms of PSD and constitutes the key factors and important indicators of a successful model (Jin et al., 2017; Niu et al., 2015; Robinson and Jorge, 2016; Vahid-Ansari et al., 2016; Verma et al., 2014; Zhang et al., 2015). However, the MCAO model inevitably results in a decline in motor and sensory ability, which makes the subjects highly susceptible to fatigue. Other than the SPT, most measurements related to motion are influenced by many factors; insufficient exercise capacity, rather than depression, can reduce activity or prolong the latency to take action (Niu et al., 2015). In addition, many patients suffer from post stroke anxiety (Nemeth et al., 2012; Niu et al., 2015; Vahid-Ansari et al., 2016), and it is a major challenge to effectively distinguish anxiety from depression. Therefore, the selection of appropriate methods to assess the core symptoms of a PSD model must be reconsidered.

Author contributions

Conceived and designed the study: X.T., S.Z., LY, J.W., C.L., and Q.W. Performed the study: X.T., W.Y., R.Q., T.F., J.W., and Q.W. Revised the paper for intellectual content: D.M. K.L, Z.Z., J.T., YM and Q.W. Wrote the paper: X.T., W.Y., T.S. and Q.W. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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