REVIEW ARTICLE

Detecting anxious symptoms related to Parkinson's disease in animal models: A review

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Abstract

There has been a significant increase in interest in anxiety in Parkinson's disease (PD) patients. Hence, patients with PD frequently experience anxiety. Anxiety, depression, and pain are typical PD symptoms. Anxiety disturbances are a common nonmotor symptom in people with PD. At the onset of the illness, non-motor symptoms may significantly influence the patient's quality of life, even before motor symptoms emerge. Animal models of PD have previously proved helpful in shedding light on some of these mysteries. However, there are insufficient trials examining the psychotropic therapy of anxiety in PD patients. Therefore, applying the anxiety model in the animal model as one of the depressive disorders seems necessary. Identifying viable treatment strategies for PD relies heavily on animal models exhibiting early disease pathology. According to our findings in this review, the elevated plus maze test is a more practical tool for detecting rodent anxiety-like behavior. In contrast, the zebrafish model employed a novel tank and light-dark box tests for behavioral analysis, and rotenone-treated zebrafish is one of the best candidates for detecting anxiety-like behavior in PD models.

Introduction

Parkinson's disease (PD) is one of the fastest-growing groups of neurodegenerative illnesses, affecting over 6.2 million people worldwide, and is anticipated to impact over 12 million by 2040 (Lama *et al.* 2021). PD is the second most common neurodegenerative condition associated with aging (Doyle & Croll 2022; Wang *et al.* 2015). The definitive treatment of Parkinson's disease has been hampered by several obstacles, despite the significant progress in developing cutting-edge treatments (Ghamgosha *et al.* 2018). PD is a complex, multisystem condition characterized by α-synuclein (SNCA) pathology, degradation of nigrostriatal dopaminergic neurons, multiple pathogenetic processes, and the manifestation of a wide variety of motor (MSs) and non-motor symptoms (NMSs) (Lama *et al.* 2021; Tinakoua *et al.* 2015). Hence, PD can be categorized into two types of symptoms. Bradykinesia (i.e., a reduction in speed to commence voluntary movement), resting tumor, stiffness, hypokinesia, and postural instability are all signs of MSs. On the other hand, NMSs include irregular sleep patterns, autonomic dysfunction (constipation and nausea), depressive disorders (anxiety and depression), and dementia (Deng *et al.* 2021a; Faivre *et al.* 2019; Moon

& Paek 2015). In treating Parkinson's disease, NMS symptoms, especially mental illnesses, are increasingly recognized as a significant obstacle (Bonito-Oliva *et al.* 2014). Hence, PD non-motor symptoms are vital to understanding, but suitable pre-clinical models are needed (Faivre *et al.* 2019). PD patients' NMS symptoms, including depressive/anxious moods, cognitive difficulties, constipation, urination problems, and sleep issues, are all common in PD patients before the onset of motor symptoms (Bassetti 2011; Niu *et al.* 2015). Anxiety disorders are a common non-motor symptom of PD (Chen & Marsh 2014). At least one-third of patients with Parkinson's disease are severely affected by anxiety (Pontone *et al.* 2019). Scientists have introduced several animal species as research models (Razali *et al.* 2021). This paper focused on NMS symptoms, especially anxiety, as applied in animal models. Also, PD is distinguished by dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc), cortex, and striatum, with an enhanced degree of α-syn pathology (Kim *et al.* 2021) and intracellular inclusions known as Lewy bodies (LB) (Pang *et al.* 2019). It has been suggested that the nucleus accumbens (NAc), a portion of the ventral striatum associated with reward and emotional processing, may have a role in neurodegenerative disorders like PD (Kim *et al.* 2021).

Identifying NMSs involves high clinical suspicion, using particular questionnaires and supplemental testing (Bassetti 2011). By analyzing the medical histories of individuals diagnosed with PD, O'Sullivan *et al.* aimed to link NMSs to PD (O'Sullivan *et al.* 2008). NMSs included urinary tracts and depressive symptoms such as depression and anxiety in 20 to 40% of patients (O'Sullivan *et al.* 2008; Walsh & Bennett 2001). As Overton and Coizet (2020) found, the prevalence of anxiety disorders in PD patients ranges from 24.5 to 46.7% (average 31%) (Overton & Coizet 2020). These neuropsychiatric abnormalities are commonly accompanied by cognitive deficits, which might be seen in the early stages of the disease (Campos *et al.* 2013). Anxiety may react to the illness's stress or be caused by the disease's neurochemical alterations (Walsh & Bennett 2001). Many people with PD have abnormal mitochondrial shapes and functions, which shows that mitochondrial dysfunction and oxidative stress (OS) plays an integral part in this disease's pathophysiology (Henchcliffe & Beal 2008). Other authors mentioned the correlation between the gut-brain axis and PD (Keshavarzian *et al.* 2015; Lai *et al.* 2018; Scheperjans *et al.* 2015). Germ-free mice that received fecal microbiota transplants from Parkinson's disease patients had comparable gut microbiota compositions to the hosts, and α-synuclein overexpressing animals transplanted with feces from a Parkinson's patient displayed motor dysfunctions (Jang *et al.* 2020). Although there is a growing body of research on the non-motor symptoms of PD, the literature on anxiety problems in PD patients and animal models of PD is limited (Vieira *et al.* 2019). Hence, we tried highlighting anxiety-like behavior in the PD animal model in this research.

Anxiety and Parkinson's disease from a neurobiology viewpoint

Anxiety in Parkinson's disease may be a physiological response to the emergence of other symptoms as the disease progresses; it may be linked to alterations in the brain's neurochemistry (Vieira *et al.* 2019). Anxiety symptoms often accompany a person's experience with PD before they manifest in their motor abilities. This condition suggests that anxiety is more than just a reaction to the psychological effects of receiving a PD diagnosis or the disorder's motor consequences (Overton & Coizet 2020). Some persons with anxiety will respond to dopaminergic therapy, while those whose dopaminergic status is not reliant on the drug will continue to suffer in silence (Khatri *et al.* 2020). As a result, it has been suggested that antiparkinsonian pharmaceuticals may be linked to increased anxiety associated with PD and the medications used to manage the illness's motor symptoms (Overton & Coizet 2020). All phases of Parkinson's disease, including the prodromal stage, are associated with depression and anxiety in 30–45 percent and 25–49 percent of patients, respectively (Kano *et al.* 2011). Anxiety incidence ranges from 20 to 40 percent, but the high prevalence of anxiety in PD is frequently undiagnosed and untreated (Upneja *et al.* 2021). In a study by Upneja *et al.* (2021), with decreasing frequency, the subtypes of anxiety in PD patients in a cohort study were seen as episodic anxiety at 50%, avoidance behavior (35%), and persistent anxiety (15%) (Upneja *et al.* 2021). Also, they discovered that anxiety is highly linked with disease characteristics, including severity ($p < 0.005$), duration of disease ($p < 0.001$), and levodopa equivalent dose ($p < 0.001$) (Upneja *et al.* 2021). However, in PD, depression and anxiety are widespread and significantly impact the quality of life (Kano *et al.* 2011).

It is difficult to distinguish between anxiety and depression, although, unlike depression, the primary characteristic of anxiety is excessive dread, typically in response to specific events or dangers (Deng *et al.* 2020; Hosseini & Modarresi Chahardehi 2022; Modarresi Chahardehi *et al.* 2017; Ostovar *et al.* 2022). Anxiety disorders are widely recognized as common mental comorbidities in PD and contribute significantly to cognitive, motor, and social performance deficits (Chen & Marsh 2014). The burden on caregivers and quality of life is negatively impacted by anxiety in people with PD (Chen & Marsh 2014). Hence, a review by Prediger *et al.* (2012) showed that anxiety disorders are frequently underdiagnosed and under-treated in PD patients, despite their high frequency and impact on quality of life (Prediger *et al.* 2012). The treatment of anxiety in patients with PD

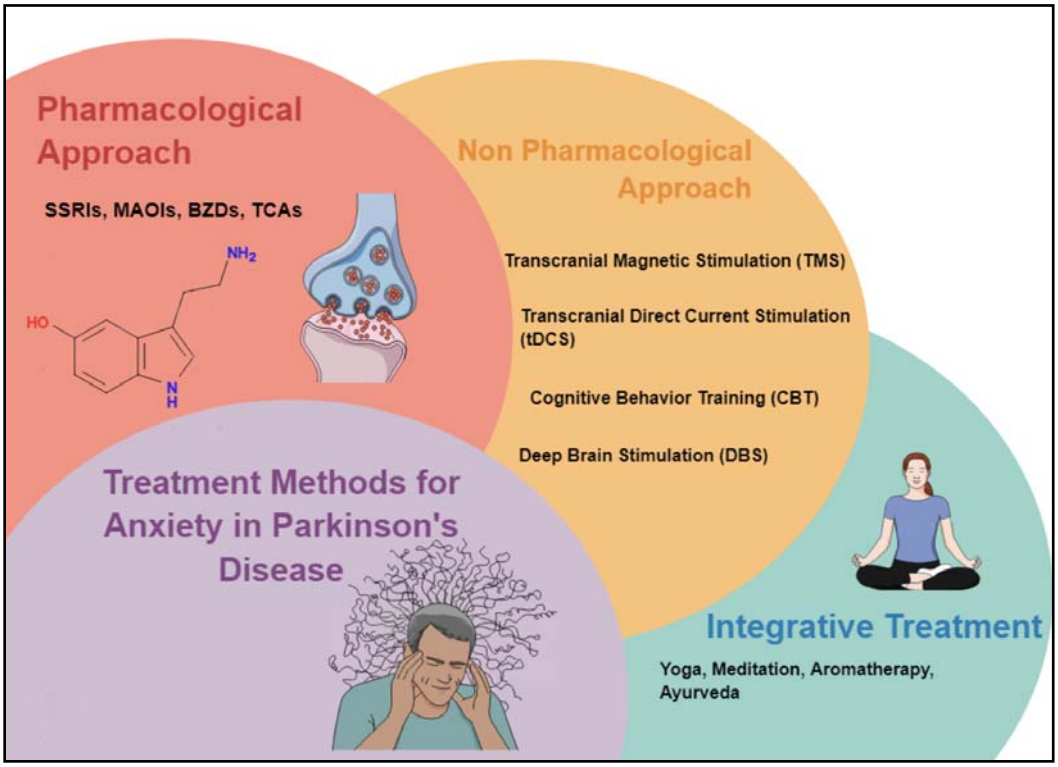

Fig. 1. Treatment approaches for anxiety in Parkinson's disease in humans

poses a significant challenge to worldwide healthcare, making it imperative to discover novel treatments to manage the condition better. Levodopa, the standard gold therapy, gives clinical relief, but its influence on neuropsychiatric consequences such as anxiety is unclear (Khatri *et al.* 2020). However, the underlying pathophysiology of these symptoms has not yet been established (Faivre *et al.* 2019). In addition to abnormalities in the dopaminergic system, including a link between striatal dopamine (DA) transporter availability and anxiety, it has been suggested that structural variations in the amygdala size lead to this symptom (Vriend *et al.* 2016). Tinakoua *et al.* (2015) found that non-motor impairments, such as anxiety and depression, in Parkinson's patients may be directly related to bilateral DA depletion (Tinakoua *et al.* 2015).

Anxiety is a frequent non-motor symptom of PD that substantially influences patients' quality of life and can complicate therapy (Vieira *et al.* 2019). On the other hand, as we discussed previously, data shows that anxiety problems in PD may be associated with neurochemical alterations, especially as we mentioned earlier about DA (Vieira *et al.* 2019). Serotonin affects various physiological and pathological states, including memory and learning, anxiety, drug misuse, depression, schizophrenia, and migraine. There are at least 14 distinct subtypes of serotonin receptors in animals. They are divided into seven groups, each with a unique alpha peptide ($5HT_1$–$5\text{-}HT_7$). The $5\text{-}HT_{1A}$ receptor subtype was the first to be isolated and studied. It is pre- and post-synaptically located and is well known for its role in anxiety and depression (Sallinen 2009). In Parkinson's patients, DA levels must be restored, and dopamine is released from 5-HT and NE neurons to maintain homeostasis. DA is released from 5-HT and NE, raising dopamine levels while displacing endogenous 5-HT and NE, the sources of anxiety. The lack of dopamine in PD causes an increase in the firing rate of the locus coeruleus (LC) neurons, inhibiting the synthesis and release of 5-HT neurons and raising anxiety levels in PD patients (Khatri *et al.* 2020). In the animal model, Vieira *et al.* (2019) discovered that the 6-OHDA-induced parkinsonism model in rats caused anxiety-like behavior that may be connected to the dysregulation of neurotransmitter systems in anxiety-associated brain regions, including the amygdala, prefrontal cortex, and striatum (Vieira *et al.* 2019). Figure 1 demonstrates some treatment methods for anxiety in PD patients.

Remarkably, the basolateral nucleus of the amygdala has been implicated for a long time in the regulation of protective behavior and, by extension, fear and anxiety. The emotional component of anxiety is integrated into the amygdala, which may be explained by the activation of the dorsal raphe nucleus, leading to a rise in 5-HT levels in the amygdala under anxious conditions. In this regard, it is essential to note that 5-HT has a distinct function in modulating anxiety (Vieira *et al.* 2019). However, six environmental risk factors for PD have a highly suggestive association: head injury, anxiety, depression, beta-blocker use, and high uric acid levels all increase the risk of PD, while smoking, physical activity, and low uric acid levels all decrease the risk (Bellou *et al.* 2016).

Anxiety disorder types in PD

In general, anxiety is not a result of the diagnostic or motoric symptoms of the condition (Overton & Coizet 2020). *Anxiety* is a psychiatric disease linked to stress's detrimental consequences (Guimarães *et al.* 2016a). Patients with PD typically exhibit generalized anxiety disorder, panic disorder, social phobia, phobic disorder, agoraphobia, and obsessive-compulsive disorder. It might manifest as generalized anxiety disorder, phobias, and panic disorder (Khatri *et al.* 2020; Overton & Coizet 2020). In some cases, people with PD may view themselves as "disfigured" and suffer substantial difficulty interacting with others, leading to social anxiety. Anxiety leads to mental and bodily pain and preexisting motor symptoms or irregularities. For instance, patients report that anxiety attacks exacerbate underlying tremors or dyskinesia, and fear of falling has been linked to poor postural stability (Chen & Marsh 2014).

A primary pathological process of PD

Even though the specific causation of PD is unknown (Khatri *et al.* 2020), decades of clinical and non-clinical PD investigations have shown several environmental, genetic, and OS variables contributing to PD risk. However, arguably the most evident is the increase in life expectancy (Ball *et al.* 2019; Razali *et al.* 2021). There is no diagnostic test for PD, and most diagnoses are based on clinical symptoms and significant responses to dopaminergic medication therapy (Ball *et al.* 2019). Hence, we can conclude that the most significant risk factor for the development of Parkinson's disease is aging (Pang *et al.* 2019). According to the researchers, mitochondrial disease of aging is another name for PD in the medical literature (Prasad & Hung 2020). A central dopaminergic deficiency and dysregulation of 5-HT and NE in the brain are two potential causes of anxiety in people with PD (Vieira *et al.* 2019), which was the primary focus of this review on anxiety disorders. From a behavioral point of view, when fluid and imaging biomarkers are absent, prodromal symptoms can be used as clinical biomarkers to identify individuals in the premotor stage. Hyposmia, sleep irregularities, autonomic dysfunction, and mental difficulties are among the symptoms; prodromal symptoms, such as anxiety, depression, cognitive impairment, and somnolence, are more common and worsen at an advanced stage (Taguchi *et al.* 2020).

Mitochondrial dysfunction in Parkinson's disease

Mitochondria are prevalent organelles that are essential for cellular survival and efficient functioning. Complex I activity in the substantia nigra of patients with Parkinson's disease (PD) was significantly lower than in age-matched controls (Schapira & Gegg 2011). Defects in mitochondrial complex-I of the respiratory chain may be the most reasonable cause of neuronal degeneration in Parkinson's disease by lowering ATP production in the cells (Moon & Paek 2015). Mitochondrial malfunction is a well-known and essential factor in this disease. This is backed by a vast and constantly expanding body of research demonstrating the central and complex nature of mitochondrial (dys)function (Prasuhn *et al.* 2021). Mitochondrial failure in PD can be caused by various factors, including impairment of mitochondrial biogenesis, increased reactive oxygen species (ROS), faulty mitophagy, impaired trafficking, and disruption of the electron transport chain (Prasuhn *et al.* 2021). As a consequence of cellular respiration, the mitochondria generate reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide anion (O_2-), hydroxyl free radical (OH), and peroxynitrite (ONO_2-). Increased levels of ROS may have a role in the development of PD (Khatri *et al.* 2020). Increased ROS production reduces the mitochondrial defense system and triggers neuronal death, which leads to Parkinson's disease (Khatri *et al.* 2020).

Familial PD is caused by several genetic abnormalities directly connected to mitochondrial malfunction. Only a few genes have been identified as monogenic causes (i.e., autosomal dominant *SNCA* and *LRRK2* mutations and autosomal recessive *Parkin*, *PINK1*, and *ATP13A2* mutations) (Ariga *et al.* 2013). The function of the PD family genes PTEN-induced putative kinase 1 (PINK1) and parkin (PRKN) in promoting mitochondrial breakdown (mitophagy) have reinforced the significance of this mechanism in the etiology of PD (Malpartida *et al.* 2021). It is now possible to target mitochondria therapeutically in PD by better understanding the role of PD-associated genes like *SNCA*, *CHCHD2*, *DJ-1*, and *LRRK2* in mitochondrial dysfunction and how they differ from those seen in sporadic forms of this disease (sPD) (Malpartida *et al.* 2021). Mutations in *LRRK2* affect mitophagy, and α-synuclein oligomers and aggregates interact with outer mitochondrial membrane substrates, resulting in mitochondrial malfunction, both of which have been linked to familial Parkinson's disease (Malpartida *et al.* 2021). *DJ-1* is the gene responsible for familial Parkinson's disease (park7) and is an oncogene (Ariga *et al.* 2013). This enzyme, *DJ-1*, has a variety of roles, including transcriptional regulation, antioxidative stress response, chaperone, protease, and mitochondrial regulation. Its oxidative state controls its activity, particularly cysteine 106 (C106) of *DJ-1* (Ariga *et al.* 2013). *DJ-1* mutations only rarely cause familial PD. This protein selectively subdivides into the mitochondrial matrix and intermembrane space in response to oxidative stress, where it can protect mitochondria against OS. On the other hand, dopaminergic nigrostriatal cell death is the current problem caused by these gene alterations (Schapira & Gegg 2011).

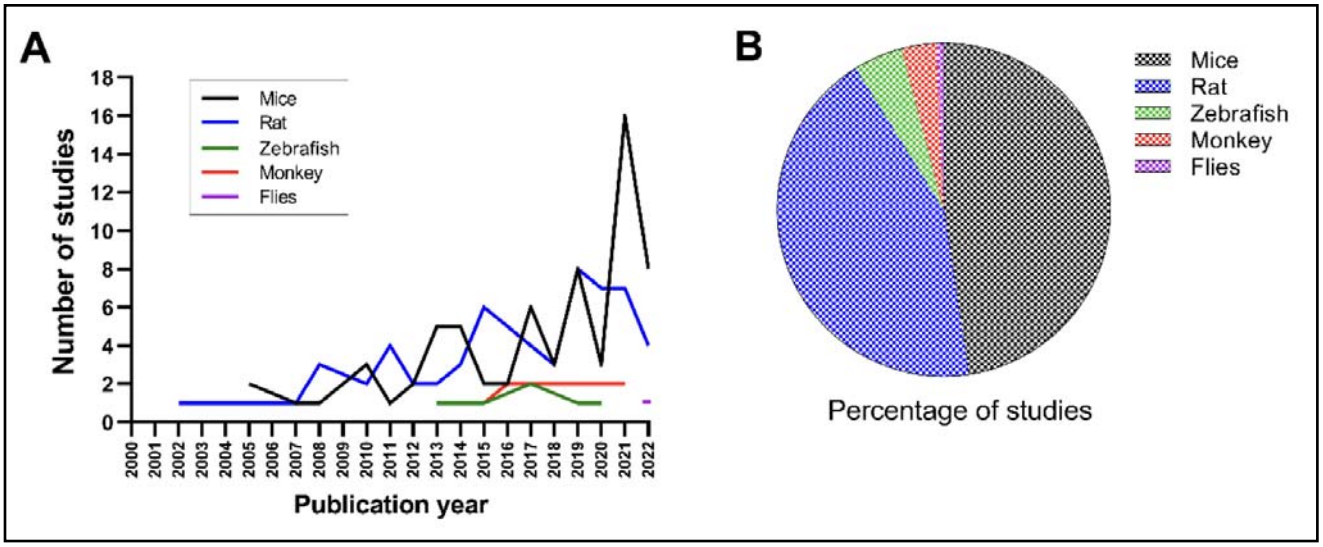

Fig. 2. A) Number of animal models used in research articles on Parkinson's disease and anxiety-like behavior published from 1985 to October 2022, including only research papers reviewed using keywords "Parkinson AND animal model AND anxiety" were obtained from the Web of Science, **B)** percentage of studies of anxiety-like behavior in PD's animal models.

Animal model research of PD

A *model organism* is an animal species distinguished by its similar physiology and anatomy, genetic homogeneity, and treatment sensitivity (Chen & Marsh 2014). Animal PD models should be able to replicate the disease's symptoms and pathology in humans (Prasad & Hung 2020). Among the PD models, locomotion has been tried the most frequently (Huntington & Srinivasan 2021). For example, the open field test is used to evaluate rats' general level of locomotor activity; the stepping test can detect akinesia, and the pole test can detect bradykinesia (Konnova & Swanberg 2018). Rats and mice are extensively investigated across biological disciplines because they are easy to care for in laboratory settings and have solid experimental protocols, including various medication delivery methods, transgenic strain development, and behavioral evaluations (Konnova & Swanberg 2018). It is possible to do mouse behavioral tests for all these symptoms, but most models have not been re-evaluated for their prevalence (Taylor *et al.* 2010). Also, the use of animal models in preclinical drug discovery studies is essential (Gamber 2016). Using non-human primates as a model species might help researchers find non-motor behavioral alterations resembling PD's early stages (Niu *et al.* 2015). However, this review focused on animal models' behavioral changes, especially anxiety. This variability demands various animal models to examine multiple perspectives on the disease (Konnova & Swanberg 2018). To research non-motor symptoms in rats, utilizing a model such as a partial nigrostriatal lesion is preferable, which may not generate concomitant motor abnormalities that might influence the test results. To evaluate sleep disruption and weight loss, sleeping, drinking, and eating habits are monitored (Konnova & Swanberg 2018). For example, the tail suspension test or the forced swim test can represent depression or behavioral despair to simulate neuropsychiatric symptoms (Taylor *et al.* 2010). In another study, Jang *et al.* (2020) observed that in a PD mouse model, acupuncture therapy at acupoints (GB34 and ST36) improved motor movements and anxiety-like behavior (Jang *et al.* 2020).

Animal models of PD and anxiety behavior

Behavioral investigations need a high degree of attention to variables relating to the environment, handling, or model (Bourin *et al.* 2007). Many animal models of PD display anxiety or depression-like behaviors (Lama *et al.* 2021). Various research has utilized laboratory animals to comprehend the etiology of anxiety and its link with stress and stressors (Guimarães *et al.* 2016a). Animal models of anxiety created for rats have been converted to mice, a more convenient and genetically diverse mammal, with conflicting results. The majority of 146 animal studies regarding Parkinson's disease and anxiety were published from 2002 to October 2022 (Fig. 2).

According to Fig. 2B, mice and rats indicated higher animal models of study at 47.62 and 43.54%, respectively, followed by zebrafish, monkeys, and flies at 4.76, 3.40, and 0.68%, respectively. Detailed descriptions of the behavioral tests related to anxiety-like behavior are provided below: The most recent animal model of anxiety in PD, which began in 2022, involves flies (Poetini *et al.* 2022).

- **Open field test:** The open field test is the most common approach utilized in behavioral research (Sestakova *et al.* 2013). For 15 minutes, mice were allowed to explore a well-cleaned photobeam activity

transparent room freely. At the beginning of the test, each mouse was carefully positioned in the center of the arena. A central section was created to detect thigmotaxis (the tendency to wander close to the walls) and anxiety-like behavior associated with time spent in the arena's center. During the 15-minute session, horizontal and vertical activity was automatically recorded, and data was analyzed at 60 to 180 seconds intervals. At the end of the test, the number of droppings was reported. The cotton pads soaked in 60% ethanol were used to clean the device immediately after each session (Bichler *et al.* 2013). According to Carola *et al.* (2004), the open-field test is better suitable for measuring motor sensitivity indices (mechanical components) than the EPM test. However, it is less sensitive to measuring psychomotor activity in rats (Carola *et al.* 2004). While both the open-field and EPM tests measure anxious behaviors, the open-field test precisely measures open-space anxiety-like behavior (Guimarães *et al.* 2016b).

- **Elevated plus maze:** Another approach frequently employed in behavioral research is the elevated plus maze test (EPM). EPM is ideal for anxiety research and is usually utilized with the open field test (Sestakova *et al.* 2013). This test is considered one of the standard assays for evaluating rodent anxiety (Guimarães *et al.* 2016b). EPM is founded on the same principle that rats have an instinctive aversion to open space as the open-field (Sestakova *et al.* 2013). In the EPM test, the animal must confront an unfamiliar environment, and it is in its nature to avoid vast expanses, which provide a potentially harmful and contradictory environment (Guimarães *et al.* 2016b). The EPM consists of a grey high-tech metal alloy labyrinth comprised of a plus-shaped device raised 60 cm with four arms (35 cm in length and 5 cm in width), two enclosed by 15 cm high walls. Mice or rats were put gently on the center platform facing a closed arm and given 5 minutes to explore the maze freely. The device was cleaned promptly after each session using ethanol-dampened cotton pads. A video-tracking system assessed the test automatically (Bichler *et al.* 2013). Therefore, decreased frequency and length of time spent in open arms correlate with elevated anxiety levels.
- **Buried test or marble burying test:** The so-called marble-burying test for mice was initially developed to evaluate anxiety-like behavior (Hoffman 2016). However, new research has challenged how the data from this test is evaluated, raising doubts about the formats usually utilized, which also cause biases that impede the interpretation of the data (Guimarães *et al.* 2016b). Animals were fed up to 90% of their body weight more than usual. The experiments began when the mice achieved a steady weight (after 3 to 4 days). The test was conducted once each day for five days (Bichler *et al.* 2013). The mouse was placed in a new cage in which a piece of honey cereal bar (about 250 mg) was concealed at the top of a clean bedding layer 0.5 cm thick and 3 cm high. The delay in digging up and starting eating was taken. Mice had a maximum of 5 minutes to discover the meal. On the sixth day, the food was placed on top of the clean bedding, and the latency to begin eating was measured (Bichler *et al.* 2013).
- **Light-dark box test:** The light-dark box test was conducted to detect anxiety-like behavior, especially in the zebrafish study. With a plastic partition, the tank (18×9×7 cm) was divided into equal-sized dark and light compartments (Wang *et al.* 2017).

Types of animal model research in PD related with anxiety-like behavior

Compared to many other neurodegenerative diseases, Parkinson's disease has a wider variety of animal models. However, it is unclear whether anxiety or depression is the most frequent non-motor symptom in PD based on previous findings in animal models (Vieira *et al.* 2019). The ideal situation would be conducting studies on the impact of currently available medications for PD and anxiety. However, there is currently no model that simultaneously screens for these two disorders (Feng *et al.* 2014). As some examples, anxiety-like symptoms in rats are caused by MPTP, 6-OHDA, and lipopolysaccharide (LPS) treatment models, but the rotenone model solely results in depressive behavior (Lama *et al.* 2021). For more details, the significant types of animal models (pharmacological, toxin, genetic, and α-synuclein) are briefly summarized (Lama *et al.* 2021) in Table 1.

Pharmacological paradigms: The study of Parkinson's disease pathology would be impossible without using pharmacological animal models (Zeng *et al.* 2018). Hence, the pharmacological models of Parkinson's disease were the first to be established, and they played a role in identifying symptomatic medications like levodopa (L-DOPA). Toxins or chemical models of Parkinson's disease can cause dopaminergic neurons in the SNpc to degenerate, leading to decreased dopamine levels in the striatum (Buhidma *et al.* 2020). Psychiatric drugs, such as reserpine and haloperidol, were first employed to create *in vivo* models of Parkinson's disease (Buhidma *et al.* 2020). Peripherally given reserpine, an inhibitor of the vesicular monoamine transporters (VMATs or VMTs), is compelling. Noradrenaline and serotonin are depleted by reserpine and dopamine, making rats severely but transiently akinetic when administered at a single dosage (Lama *et al.* 2021). The VMTs are membrane-bound proteins that transport monoamines into synaptic vesicles through a proton gradient. Among the two paralogs (VMAT1 and VMAT2, renamed Solute Carrier 18A1 and A2 (SLC18A1 and SCL18A2)), VMT1 has a higher level of expression outside of the central nervous system, predominantly in endocrine cells, as well as chromaffin and enterochromaffin cells, transporting serotonin, epinephrine, and norepinephrine (Sveins-

Tab. 1. The significant types of animal models in Parkinson's disease associated with anxiety-like behavior

Types of models	Type of animal	Test	Characteristics	References
Pharmacological paradigm				
Reserpine	mice	OFT, EPM	Increased anxiety-like behavior	(Silva-Martins et al 2021)
Haloperidol	mice	OFT	No anxiety behavior reported	(Lama *et al.* 2021)
	rat	OFT	Combined treatment of trihexyphenidyl (TPH), respeine and caffeine did not induce anxiety-like behavior	(Moo-Puc *et al.* 2004)
	rat	OFT, EPM	Induce anxiety-like behavior	(Barroca *et al.* 2019)
Lipopolysaccharide (LPS)	rat	EPM	Increased anxiety-like behavior as a sign of significant reduction in the time spent in the open arms	(Hritcu & Ciobica 2013)
	mice	OFT	Induced anxiety-like behavior	(Deneyer *et al.* 2019)
	mice	EPM	Induced anxiety-like behavior	(Song *et al.* 2019)
	mice	OFT	Induce anxiety-like behavior	(Deng *et al.* 2021b)
	mice	OFT	No induce anxiety-like behavior	(Deng *et al.* 2021a)
Alcohol	zebrafish	LDB	Induce anxiety-like behavior	(Li *et al.* 2015)
Toxin paradigm				
6-hydroxydopamine (6-OHDA)	rat	EPM	Injection of 6-OHDA elicited anxiety-like behavior.	(Vieira *et al.* 2019)
	rat	EPM, social interaction	Increased anxiety-like behavior	(Eskow *et al.* 2012)
	rat	OFT	Electropuncture as a treatment alleviated anxiety-like behavior	(Yu *et al.* 2020)
	rat	-	Induced anxiety-like behavior	(Chen *et al.* 2011)
	rat	EPM	Apamin (0.1 or 0.3 mg/kg i.p.) reduced anxiety-like behavior	(Chen *et al.* 2014)
	rat	OFT, EPM	Induced anxiety-like behavior	(Silva *et al.* 2016)
	rat	EPM	MK-801 decreased anxiety-like behavior	(Singh *et al.* 2017)
	rat	EPM	All dopaminergic (DA) agonists decreased anxiety-like behavior	(Carnicella *et al.* 2014)
	rat	EPM	L-dopa (20 mg/kg) and benserazide (5 mg/kg) not induced anxiety-like behavior	(Loiodice *et al.* 2019)
	rat	EPM	Selanik (a peptide) decreased level of anxiety with toxicity damage of DA neurons	(Slominsky *et al.* 2017)
	rat	OFT	Using high frequency deep brain stimulation of the subthalamic nucleus (STN-DBS) increased line crossing in the OFT	(Inan *et al.* 2016)
	rat	EPM	Aqueous extract of *Albizia adianthifolia* alleviated anxiety-like behavior	(Beppe *et al.* 2015)
	rat	OFT, EPM	Induced anxiety-like behavior	(Jungnickel *et al.* 2011)
	rat	OFT, EPM	Induced anxiety-like behavior	(Hui *et al.* 2015)
	rat	OFT, LDB	Senktide, a potent neurokinin-3 receptor (NK3-R) agonist did not affect anxiety-like behavior	(Chao *et al.* 2015)
	rat	OFT	Sarizotan did not affect anxiety-like behavior	(Zhang *et al.* 2011)
	rat	EPM	Using a probiotic (*Lacticaseibacillus rhamnosus* HA-114) no impact on anxiety-like behavior	(Xie & Prasad 2020)

Types of models	Type of animal	Test	Characteristics	References
6-hydroxydopamine (6-OHDA)	rat	OFT	Induce anxiety-like behavior	(Feng *et al.* 2020)
	rat		Fluvoxamine maleate increased anxiety-like behavior in early life stress.	(Dalle *et al.* 2016)
	rat	OFT, EPM	Botulinum neurotoxin-A (BoNT-A) application did not show significant anxiety-like behavior as compared with sham group.	(Antipova *et al.* 2021)
	rat	EPM	Neuropeptide S reduced anxiety- like behavior	(Sinen *et al.* 2021)
	rat	-	No anxiety behavior appeared, and decreased in striatal dopamine levels (36%).	(Branchi *et al.* 2008)
	mice	EPM, LDB	Mice exhibiting increased anxiety-like behavior after circuit-specific catecholamine denervation	(Ferrazzo *et al.* 2019)
	mice	OFT	CB2 agonist GW842166x reduced anxiogenic-like behavior	(Liu *et al.* 2022)
	rat	EPM	Increased anxiety-like behavior	(Campos *et al.* 2013)
	rat	EPM	Increased anxiety-like behavior	(Tadaiesky *et al.* 2008)
	zebrafish	Locomotor behavioral test (tank)	Induce anxiety level	(Feng *et al.* 2014)
Rotenone	zebrafish	LDB	Increased anxiety-like behavior	(Wang *et al.* 2015)
	zebrafish	LDB	Induce anxiety-like behavior	(Wang *et al.* 2017)
	rat	EPM	Vortixetine did not affect anxiety-like behavior	(Nemutlu Samur *et al.* 2022)
	rat	OFT, EPM	Activation of MT2 receptor agonist, 8-M-PDOT (10 μg/mL) induced anxiety-like behavior	(Noseda *et al.* 2016)
Paraquat	rat	EPM	Increased anxiety-like behavior	(Campos *et al.* 2013)
	zebrafish	Y-maze task	No induce anxiety-like behavior	(Bortolotto *et al.* 2014)
	zebrafish	LDB	Induced anxiety-like behavior	(Nunes *et al.* 2017)
Paraquat+maneb	rat	EPM	Increased anxiety-like behavior	(Tinakoua *et al.* 2015)
	mice	OFT (Novel open test)	Increased anxiety-like behavior	(Litteljohn *et al.* 2008)
MPTP	mice	LDB, EPM	Increased anxiety-like behavior	(Xia *et al.* 2018)
	mice	LDB	Increased anxiety-like behavior	(Mitsumoto *et al.* 2019)
	mice	EPM	Ethanol extract of *Gynostemma pentaphllum* at 50 mg/kg showed anxiolytic effect on mice	(Shin *et al.* 2014)
	mice	-	Not able to detect any difference in anxiety	
	mice	EPM, LDB	No changes were observed in anxiety	(Vuckovic *et al.* 2008)
	mice	EPM	Exercise reduced anxiety on the EPM test, while MPTP increased anxiety in the marble-burying test.	(Gorton *et al.* 2010)
	mice	EPM	Muscimol microinjections bilaterally inhibiting anterior cingulate cortex (ACC) dramatically decreased mechanical hypersensitivity and anxiety-like reactions.	(Zhou *et al.* 2021)
	mice	OFT	Long interval MPTP-induced chronic PD and anxiety-like behavior	(Ma & Rong 2022)

Types of models	Type of animal	Test	Characteristics	References
MPTP	mice/rat	EPM	1-[2-(4-benzyloxyphenoxy)ethyl] imidazole (BPEI) or safinamide alleviated anxiety-like behavior	(Chung *et al.* 2015)
	mice	OFT	Varenicline, an α4β2 nAChR partial agonist did not induce anxiety-like behavior	(Ribeiro-Carvalho *et al.* 2021)
	mice	OFT	Induced anxiety-like behavior	(Janakiraman *et al.* 2017)
	mice	EPM	Using simvastatin at 10 mg/kg decreased anxiety-like behavior	(Yan *et al.* 2020)
	rat	EPM	Simvastatin reduced anxiety-like behavior	(Yan *et al.* 2011)
	rat	-	Induced anxiety-like behavior	(Levitskaia *et al.* 2002)
	zebrafish	NTT	MPP+ reduced anxiety-like behavior in zebrafish larvae	(Christensen *et al.* 2020)
	zebrafish	NTT	Induce anxiety-like behavior	(Selvaraj *et al.* 2019)
	monkey	-	3,4-methylenedioxy-N-methamphetamine (MDMA) had an impact on anxiety.	(Sgambato 2021)
Genetic paradigm				
PINK1	rat	EPM	Induced anxiety-like behavior	(Hoffmeister *et al.* 2021)
	mice	EPM	No anxiety-like behavior using Parkin-/- mice	(Staff 2015)
	rat	Cat-odor avoidance test	Induced anxiety-like behavior	(Grigoruta *et al.* 2020)
LRRK2	mice	OFT	No induce anxiety-like behavior	(Bichler *et al.* 2013)
	mice	OFT	R1441G HOM Tg mice exhibited less anxiety-related behavior	(Chen & Wu 2022)
PARK7	mice	OFT, EPM	PARK7-/- mice exhibited anxiety-like behaviors that were mitigated by local D2 receptor pharmacology.	(Li *et al.* 2019)
PED/PEA-15 (tgPED)	mice	EPM	tgPED induced anxiety as type of diabetic 2	(Perruolo *et al.* 2016)
CHRNA7	mice	OFT	No induce anxiety	(Yin *et al.* 2017)
NF-κB/c-Rel	mice	OFT	Induced anxiety-like behavior	(Parrella *et al.* 2022)
Vesicular monoamine transporter 2 (*Vmat2*) knockdown	zebrafish	NTT	Heterozygous Vmat2 mutant zebrafish exhibited anxiety-like behavior.	(Wang *et al.* 2016)
	mice	EPM	MAT2-overexpressing mice show improved outcomes on anxiety and depressive-like behaviors	(Lohr *et al.* 2014)
NURR1	mice	OFT, EPM	No anxiety detected	(Montarolo *et al.* 2019)
D3RKO	mice	OFT	Induced anxiety-like behavior	(Moraga-Amaro *et al.* 2014)
Pitx3 (416insG)	mice	EPM	Reduced anxiety-like behavior	(Rosemann *et al.* 2010)
α-synuclein paradigm				
Adeno-associated viral vectors (AAVs)	rat	EPM	Injection of AAV a-syn caused anxiety-like behavior	(Campos *et al.* 2013)
AAV or α-syn	rat	EPM	Induced hype anxious state	(Cinar *et al.* 2020)

Types of models	Type of animal	Test	Characteristics	References
α-syn	monkey	Anxious behavior examination	Increased stereotypic behaviors and sign of anxiety	(Niu *et al.* 2015)
	mice	OFT	Environmental enrichment dramatically reduced locomotor hyperactivity and anxiety in the early stages.	(Kim *et al.* 2021)
	mice	OFT	A53T α-syn mice showed inceased anxiety-like behavior under normal condition	(Kim *et al.* 2014)
	mice	OFT	A53T mice reduced anxiety-like behavior	(Paumier *et al.* 2013)
	mice	OFT	A30P α-syn show increased anxiety-related behavior that was reversed following doxycycline (dox) treatment	(Marxreiter *et al.* 2013)
	mice	OFT	Increased anxiety-like behavior	(Wang *et al.* 2018)
	mice	OPT	Increased anxiety-like behavior	(Uemura *et al.* 2021)
	mice	EPM	A53T α-synuclein reduced anxiety	(Rothman *et al.* 2013)
	mice	OFT, EPM	Decreasing anxiety-like behavior using α-syn BAC tg mice	(Yamakado *et al.* 2012)
	mice	OFT, LDB	Induced anxiety-like behavior	(Pavia-Collado *et al.* 2021)
	mice	OFT	Using Dl-3-n-butylphthalide (NBP) decreased anxiety-like behavior	(Li *et al.* 2021)
	mice	OFT, EPM	Induced anxiety-like behavior	(Fortuna *et al.* 2017)
	mice	OFT, EPM	Induced anxiety-like behavior	(Graham & Sidhu 2010)
	rat	EPM	No induce anxiety-like behavior	(Campos *et al.* 2013)
	rat	OFT, LDB	Obesity induced anxiety-like behavior but no changes in motor activity	(Bittencourt *et al.* 2022)

EPM: Elevated plus maze test, LDB: Light-dark box test, OPT: Olfactory preference test, OFT: Open field test, NTT: Novel tank test

dottir *et al.* 2022). VMAT2, on the other hand, is mainly found in the central nervous system. Depressive disorders (depression and anxiety), drug addictions, stress, and Parkinson's disease are all linked to changes in the VMAT2 (Sveinsdottir *et al.* 2022). However, one of the main drawbacks of pharmacological models is the absence of pathology connected to Parkinson's disease (Buhidma *et al.* 2020).

Toxin paradigms: Exposure of rats or non-human primates to neurotoxins such as 6-OHDA, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Yazdani *et al.* 2006), and agrochemicals such as the pesticide rotenone (Betarbet *et al.* 2000), the herbicide paraquat (Przedborski & Ischiropoulos 2005), and the fungicide maneb are examples of neurotoxin-based methods (Konnova & Swanberg 2018). Herbicides, for example, are linked to an increased risk of PD in several epidemiological studies (Campos *et al.* 2013; Wang *et al.* 2017). In rats, the rotenone pesticide can cause Parkinson's-like symptoms, but little research has studied whether zebrafish can be used as an animal PD model (Wang *et al.* 2017). Since it was recognized that the neurotoxic MPTP induces parkinsonism in humans, it has been used to imitate the disease in rats and non-human primates (Song *et al.* 2015). In rats with no motor impairments, paraquat and maneb caused non-motor behaviors (Tinakoua *et al.* 2015). In zebrafish, neurotoxins have been found to cause symptoms similar to Parkinson's disease (Feng *et al.* 2014). However, the etiology of Parkinson's disease in humans cannot be fully replicated in the zebrafish because neurotoxins like MPTP and 6-OHDA fail to cause aggregation of α-synuclein (Zeng *et al.* 2018). There has been little research into bilateral 6-OHDA injections in the striatum, and the available data is highly contradictory. For example, one study revealed that wounded rats exhibited a depressive-like condition, decreased anxiety-like behavior, and changes in social behavior but no changes in cognitive functioning (Branchi *et al.* 2008). To induce the PD-like lesion in male Wistar rats, Vieira *et al.* (2019) delivered 6 g of 6-OHDA in 1 L of artificial cerebrospinal fluid (at 0.33 L/min) injected intranigrally. The injection of 6-OHDA induced anxiety-like behavior in the elevated plus-maze, and contextual fear conditioning tests were undertaken on days 21 and 24, respectively (Vieira *et al.* 2019). Anxiety in PD may be linked to abnormal monoamine levels in the amygdala, hippocampus, and cortex (Vieira *et al.* 2019). The neurotoxin MPTP is commonly used in animal experiments as a model for PD, causes an increase in

α-synuclein, and alters the gut microbial ecology, especially in the Proteobacteria phylum (Lai *et al.* 2018).

Genetic paradigms: Transgenic models and viral vector-mediated models based on genes associated with monogenic Parkinson's disease, such as *SNCA*, *LRRK2, UCH-L1, PRKN, PINK1*, and *DJ-1*, as well as modification of dopaminergic transcription factors, are used to simulate Parkinson's disease, as we mentioned previously (Konnova & Swanberg 2018), due to the finding of more than 13 loci in 9 distinct genes associated with familial forms of PD (Buhidma *et al.* 2020). In this model, Fleming *et al.* (2008) found that using Thy1 promotor in transgenic mice overexpressing wild-type α-syn exhibited hyposmia and the inclusion of insoluble α-syn in the olfactory bulb. Anxiety manifests at four months, sleep disturbances at nine to ten months, and colonic dysfunction at one year (Fleming *et al.* 2008). However, in a rat model, wild-type α-syn BAC transgenic animals demonstrated olfactory impairment at three months. At six months, they had a 30% drop in DA content in the striatum, followed by the motor phenotype at 16 months. In addition, they displayed anxiety-like behaviors, yet there were no significant changes in noradrenaline and serotonin levels (Nuber *et al.* 2013).

α-synuclein paradigms: Following adeno-associated virus (AAV)-mediated expression of a-syn in mice, the early pre-symptomatic stage coincides with early striatal impairment, which may come before non-motor behavioral alterations resembling prodromal symptoms like anxiety or depression (Huntington & Srinivasan 2021). In addition, the α-syn animal model exhibited a decrease in exploratory behavior. However, the 6-OHDA and using paraquat in animals exhibited a substantial increase in both depressive-and anxiety-like behaviors (Campos *et al.* 2013). A small but significant number of the α-syn transgenic mice generated have been unable to mimic critical pathogenic aspects such as the gradual loss of nigrostriatal dopaminergic neurons and neurites. AAV and lentivirus have been utilized to overexpress α-syn in rats, and these models have duplicated numerous PD-like pathology characteristics (Song *et al.* 2015). The substantia nigra of rats was injected with lentiviral vectors expressing distinct human or rat versions of α-syn to construct a PD animal model (Lo Bianco *et al.* 2002).

Figure 3 exhibits the most preferred paradigms (in rodents) found in research papers for identifying anxiety in animal models of Parkinson's disease.

Zebrafish: new era in Parkinson's animal model associated with anxiety

In addition, non-motor symptoms of PD, such as depression, anxiety, and emotional abnormalities, are difficult to imitate in rat models of PD (Modarresi Chahardehi *et al.* 2019; Niu *et al.* 2015). In studying human brain problems and neuropharmacology, the zebrafish offers a novel vertebrate model to be explored further (Wang *et al.* 2016). They may also develop complicated connections and have well-documented emotions of fear and anxiety (Doyle & Croll 2022). Zebrafish research has utilized a variety of neurotoxins, including MPTP, 6-OHDA, and paraquat, to elicit PD-like symptoms for decades (Razali *et al.* 2021). The zebrafish's transparent skull and brain during larval development, which allows *in vivo* fluorescence imaging of activity in vast populations of cells, is a crucial benefit in neuroscience

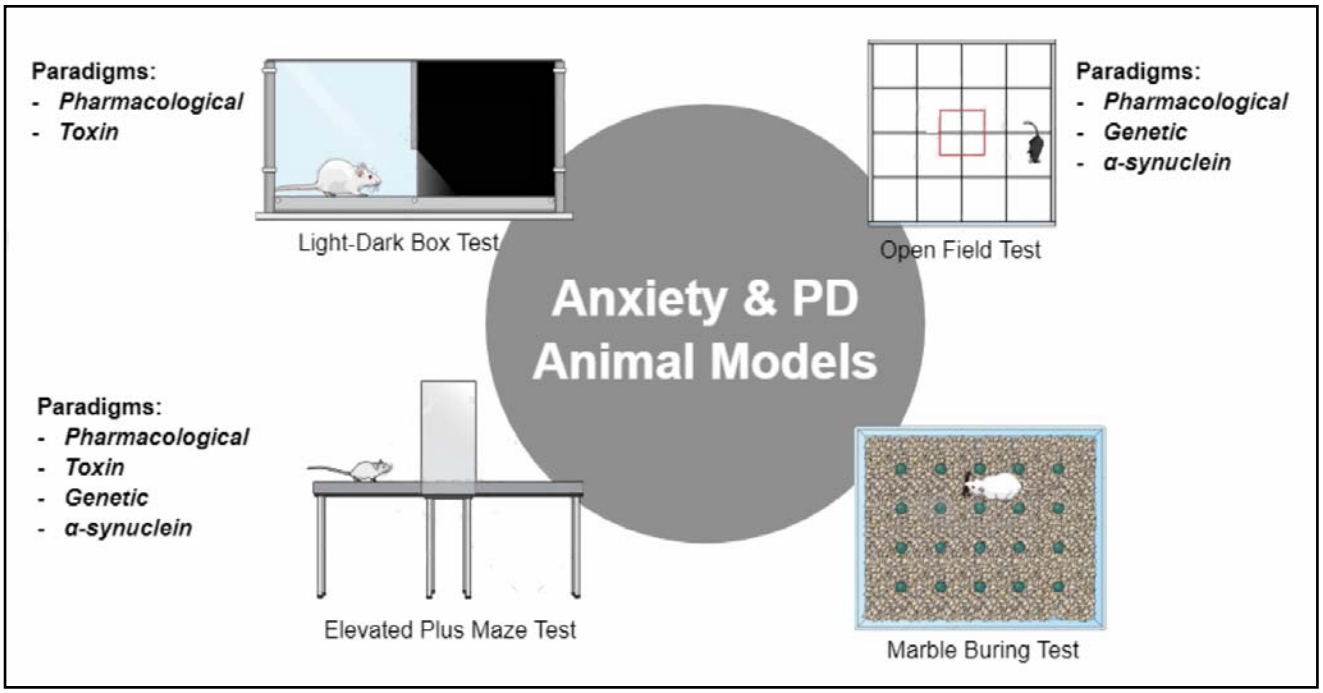

Fig. 3. Preferred paradigms are employed for detecting anxiety in an animal model of Parkinson's disease

research (Cheng *et al.* 2011; Modarresi Chahardehi *et al.* 2020). Because of this, Streisinger thought it was conceivable to examine the neurological development of vertebrates, a field in which information was restricted due to underdeveloped procedures and inappropriate animal models (Barros *et al.* 2008). On the other hand, it has been shown that zebrafish orthologs and human neurodegenerative disease models share several morphological, physiological, and biochemical abnormalities in specific neuronal populations (Razali *et al.* 2021). For example, in the light-dark box test, an indicator of increased or decreased swimming activity can be used with anti-anxiety effects (extended time in the white compartment) (Maximino *et al.* 2010).

There are few genetic zebrafish models for anxiety, although the DISC1 gene and the GR mutation cause a depression-like phenotype in zebrafish (Wang *et al.* 2016). The AB wild-type zebrafish strain is the best for studying anxiety and aggression because of its high cortisol hormone levels in the brain (Oliveira 2013). In a study by Wang *et al.* (2015) for detecting anxiety in a PD model, it was demonstrated that using the light-dark box test, zebrafish were treated with rotenone (2 μg/L) for four weeks and developed anxiety and depression behaviors. In addition, the same study found that rotenone-treated zebrafish had poor olfaction, which is another prominent non-motor sign of PD (Wang *et al.* 2015). Rotenone inhibits mitochondrial complex I and causes the death of dopaminergic neurons. Its dopaminergic neurotoxicity depends on DA metabolism and redistribution from vesicles to the cytoplasm (Watabe & Nakaki 2007). In contrast, NMS behaviors, such as anxiety and social interactions, were not altered in zebrafish treated with paraquat (Bortolotto *et al.* 2014). On the other hand, vesicular monoamine transporter 2 (Vmat2) is found scattered in the central nervous system and is responsible for vesicular transmitter uptake. However, the relationship between Vmat2 deficiency and anxiety is infrequently explored, particularly in zebrafish (Wang *et al.* 2016). These data imply that the Vmat2 heterozygous mutant zebrafish might represent a novel model for anxiety, which may be connected to the reduced levels of DA, 5-HT, and norepinephrine (Wang *et al.* 2016). Hence, for future study, it might be interesting to associate subjects between this transporter in zebrafish with the PD model in this organism.

Conclusion

Researchers have studied Parkinson's disease for many years, focusing on both the motor symptoms and the dopamine system. Based on previous studies, the elevated plus maze test is one suitable method to detect anxiety-like behavior in animal PD models. Thus, based on the latest studies, zebrafish may be a helpful alternative model for studying the genetic basis of Parkinson's disease. It appears that rotenone-treated zebrafish are an appropriate model for PD associated with anxiety inducers. However, we could more effectively detect rodent anxiety-like behavior using the elevated plus maze test. On the other hand, the zebrafish model used a novel tank and light-dark box for testing instead.

Compliance with Ethical Standards

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Author's contribution
AMC wrote and organized the first draft; YH and SMM helped in providing data, YM and IN checked the latest version of manuscript. All authors read and approved the final manuscript.

Conflict of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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