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Research Article

Age-Dependent Effects of Paraquat-Induced Parkinsonism on Neurobehaviour in Male Wistar Rats

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Abstract

Background: Paraquat (PQ), a widely used herbicide, is implicated in Parkinson's disease (PD)-like neurodegeneration via oxidative stress mechanisms. Age is a critical factor influencing susceptibility to neurotoxins. This study examined the age-dependent effects of paraquat-induced Parkinsonism on neurobehavioural outcomes in male Wistar rats.

Methods: Sixty-three male Wistar rats were stratified into juvenile, young-adult, and adult cohorts and randomly assigned to control, paraquat, or PQ+Recovery groups (n = 7 per group). Paraquat (10 mg/kg, i.p.) was administered biweekly for three weeks; recovery groups were monitored for an additional two months. Neurobehavioural assessments including hanging wire, open field, and Y-maze tests, were conducted at baseline, post-exposure, and post-recovery. Data were analyzed using t-tests and ANOVA ($p \leq 0.05$).

Key Findings: Spontaneous alternation showed no significant differences across age groups. Latency-to-fall remained unchanged in juvenile and young-adult rats but declined significantly in adult PQ+Recovery animals ($p = 0.05$). Adult paraquat-exposed rats exhibited reduced line crossings ($p = 0.02$). Urine pool frequency decreased significantly in young-adult paraquat ($p = 0.0010$) and PQ+Recovery groups ($p = 0.0016$), with notable group effects in young-adult ($p = 0.007$) and juvenile cohorts ($p = 0.047$).

Conclusion: Paraquat exposure induces mild but age-dependent neurobehavioral impairments in male Wistar rats, with adult animals exhibiting the greatest vulnerability. These findings underscore the importance of age as a determinant in neurotoxicological risk and support the use of age-stratified models in Parkinsonism research.

Keywords: Paraquat, Parkinsonism, Age-dependence, Neurobehaviour, Wistar rats.

Introduction

Parkinson disease (PD) is a chronic, progressive neurodegenerative disorder and the second most prevalent neurological condition globally, affecting over 6 million individuals and approximately 1% of those above 60 years of age [1,2]. Clinically, PD is characterized by hallmark motor symptoms—bradykinesia, rigidity, resting tremor, and postural instability—as well as a spectrum of non-motor features including cognitive decline, depression, sleep disturbances, paresthesia, and autonomic dysfunction [3,4,5]. These motor impairments primarily result from the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to dopamine depletion in the striatum and disrupted motor coordination.

Both biological and demographic factors, particularly sex and age, significantly influence PD risk and progression. Epidemiological data show higher incidence and severity in males, potentially due to hormonal differences and elevated α-synuclein accumulation, while estrogen appears neuroprotective via antioxidant and anti-inflammatory pathways. Aging remains the most prominent risk factor, as it compromises mitochondrial function, impairs proteostasis, and increases oxidative stress, thereby accelerating alpha-sunuclein aggregation and dopaminergic neurodegeneration.

PD etiology involves both genetic predisposition and environmental exposures [6,7]. Among environmental toxins, paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) which is a widely used herbicide, has garnered attention due to strong epidemiological and experimental links to PD-like pathology [8,9]. Paraquat induces oxidative stress through redox cycling, generating reactive oxygen species (ROS), impairing mitochondrial electron transport, and mimicking key features of idiopathic PD [10,11].

Rodent models, particularly Wistar rats, are widely employed to study paraquat-induced neurodegeneration due to their well-characterized neuroanatomy and behavioral responsiveness. Following paraquat exposure, rats exhibit PD-like features including dopaminergic neuronal loss in the Substantia Nigra pars compacta, increased biomarker expression, and motor deficits. Behavioral assays such as the rotarod, open field, and cylinder test assess locomotor coordination and asymmetry, while pole and stepping tests evaluate bradykinesia [12,13,14]. Cognitive and affective impairments are measured using the Y-maze, Novel Object Recognition, and sucrose preference tests [15,16,17].

Despite paraquat's established neurotoxicity, most studies have focused on adult animals, leaving the age-dependent nature of its effects underexplored [18,19,20,21]. This is a critical gap, as aging modulates mitochondrial resilience, proteasomal efficiency, and biomarker dynamics which are factors that may influence susceptibility to neurotoxins. Moreover, recovery dynamics post-exposure remain poorly understood, though they are essential for evaluating the reversibility of neurotoxic effects and identifying potential windows for neurorestoration.

This study addresses these gaps by investigating the age-dependent effects of paraquat-induced Parkinsonism on neurobehaviour in juvenile, young-adult, and adult male Wistar rats. It further evaluates recovery outcomes following a two-month post-exposure period. This integrative, age-stratified, and recovery-focused approach aims to clarify how paraquat toxicity and neurorestorative processes evolve across developmental stages. We hypothesize that paraquat induces age-dependent neurobehavioral impairments, and that younger animals exhibit greater capacity for functional recovery following toxic insult.

Materials and Methods

This study was conducted in the Department of Anatomy, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Nigeria, over a three-month period from June to August 2025. All experimental procedures were reviewed and approved by the Animal Research Ethics Committee of Nnamdi Azikiwe University, Awka (Reference Number: NAU/AREC/2025/0059; issued 12th May 2025), and were carried out in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals.

A total of 63 apparently healthy male Wistar rats were used in this study. The animals were obtained from the nursery animal facility of the College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, Abia State. Prior to experimental exposure, the rats were stratified into three age-based cohorts: Juvenile (6–8 weeks old), Young Adult (>8–12 weeks old), and Adult (>12 weeks old). Although some juvenile rats transitioned into later developmental stages during the 13-week study period, group classification was maintained based on baseline age to ensure consistency in experimental comparisons.

Within each age cohort, animals were randomly assigned to one of three experimental groups, each consisting of seven rats. The control group received intraperitoneal injections of normal saline (10 mg/kg body weight). The paraquat (PQ) group received paraquat dichloride (10 mg/kg body weight, intraperitoneally) twice weekly for three consecutive weeks. The PQ+Recovery group received the same paraquat treatment regimen, followed by a two-month recovery period before sacrifice. The two-month recovery interval was selected based on the pharmacokinetics of paraquat, which has a reported half-life of approximately one month in the ventral midbrain of mice. This extended duration was intended to allow for substantial paraquat clearance and to facilitate the assessment of both immediate and long-term neurotoxic effects.

All animals were housed in standard polypropylene cages lined with wood shavings and maintained under ambient conditions at a temperature of 22 ± 2 °C and standard humidity, with a 12-hour light/dark cycle. They were provided ad libitum access to standard laboratory rat chow and clean drinking water. Cages and bedding were changed three times weekly. Prior to the commencement of the experiment, animals were acclimatized for two weeks, during which daily health checks were conducted to ensure their suitability for the study.

Induction of Parkinsonism

To induce Parkinsonism, paraquat dichloride (1,1′-dimethyl-4,4′-bipyridinium dichloride; analytical grade, Sigma-Aldrich, USA) was utilized. A concentrated stock solution of 200 mg/mL was procured and diluted to a working concentration of 10 mg/mL by combining one part of the stock with 19 parts of normal saline. Specifically, 1 mL of the stock was mixed with 19 mL of saline to yield 20 mL of the desired working solution. Fresh dilutions were prepared on each day of administration to ensure potency and consistency. Paraquat was administered intraperitoneally at a dose of 10 mg/kg body weight, twice weekly for three consecutive weeks, in accordance with the protocol established by Tariq et al. [22]. Prior to each injection, animals were weighed to ensure accurate dosing. Control animals, matched by age, received equivalent volumes of normal saline as a vehicle control.

Following the final paraquat exposure, animals in the PQ+Recovery group were monitored for an additional two months to assess potential long-term neurobehavioral effects. Throughout the study, animal health and survival were closely observed and documented.

Neurobehavioral Assessments

Behavioral evaluations were conducted at three time points: prior to paraquat administration (baseline), 24 hours after the final injection, and at the conclusion of the recovery period for the PQ+Recovery group. All assessments were carried out during the light phase (09:00–14:00 hr) in a sound-attenuated environment. To eliminate olfactory cues, all testing apparatus were sanitized with 70% ethanol between trials.

The hanging wire test was employed to evaluate grip strength, neuromuscular endurance, and motor coordination. Each rat was placed on a horizontal metal wire suspended 50 cm above the ground, and the time taken to fall (latency-to-fall) was recorded, with a maximum cut-off time of 240 seconds. Longer latencies were interpreted as indicators of better motor performance [23].

Locomotor activity and stress-related behavior were assessed using the Open Field Test (OFT). The apparatus consisted of a square arena measuring 100 × 100 × 40 cm, with the floor marked into equal squares. Each rat was placed in the center of the arena and allowed to explore freely for five minutes. Observational parameters included the number of line crossings (defined as all four paws crossing into a new square) and the number of urine pools. Increased locomotion and reduced urination were interpreted as signs of enhanced exploratory behavior and reduced anxiety, respectively [24].

Spatial working memory was evaluated using the Y-maze, which comprised three arms (each 40 × 10 × 15 cm) arranged at 120° angles. Rats were placed at the end of one arm and allowed to explore the maze for five minutes. Spontaneous alternation behavior was recorded when a rat entered all three arms in sequence without repeating a previous arm (e.g., A → B → C). An entry was counted when all four paws crossed into an arm beyond the central zone. Higher alternation percentages were considered indicative of better spatial working memory [25].

Statistical Analysis

All results were expressed as mean ± standard deviation (SD). To evaluate within-group changes in neurobehavioral performance before and after treatment, paired t-tests were applied to each treatment group (control, paraquat, PQ+Recovery) within each age cohort (juvenile, young adult, adult). To assess treatment effects across age groups while accounting for repeated measures, a repeated-measures two-way ANOVA was conducted. Additionally, one-way ANOVA was used to analyze treatment effects within individual cohorts. All statistical analyses were performed using GraphPad Prism version 10.0 and IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p \leq 0.05$, and exact p-values are reported for primary outcomes.

Results

Alternation Percentage

Adult Cohort:

No significant differences were observed between pre- and post-treatment alternation percentages in the control ($p = 0.166$, Cohen's $d = -0.757$), paraquat ($p = 0.530$, $d = 0.307$), or PQ+Recovery ($p = 0.307$, $d = 0.784$) groups. Repeated-measures ANOVA revealed no significant main effects of time ($F(1,18) = 0.1637$, $p = 0.7505$), group ($F(2,18) = 0.2398$, $p = 0.9043$), or time × group interaction ($F(2,18) = 1.598$, $p = 0.3120$). [Figure 1i].

Young-Adult Cohort:

Similarly, alternation scores did not differ significantly pre- and post-treatment in the control ($p = 0.187$, $d = -0.711$), paraquat ($p = 0.524$, $d = -0.311$), or PQ+Recovery ($p = 0.913$, $d = -0.059$) groups. No significant effects of time ($F(1,18) = 2.366$, $p = 0.1822$), group ($F(2,18) = 0.1762$, $p = 0.9413$), or interaction ($F(2,18) = 0.9625$, $p = 0.5093$) were observed. [Figure 1ii].

Juvenile Cohort:

Although within-group comparisons showed no significant changes in alternation scores for control ($p = 0.266$, $d = 0.681$), paraquat ($p = 0.087$, $d = 1.011$), and PQ+Recovery ($p = 0.827$, $d = -0.144$) groups, a significant time × group interaction was detected ($F(2,18) = 6.877$, $p = 0.0124$). Post-hoc Tukey analysis revealed that PQ+Recovery animals performed significantly better than paraquat-treated animals ($p < 0.05$), though their performance remained below control levels. [Figure 1iii].

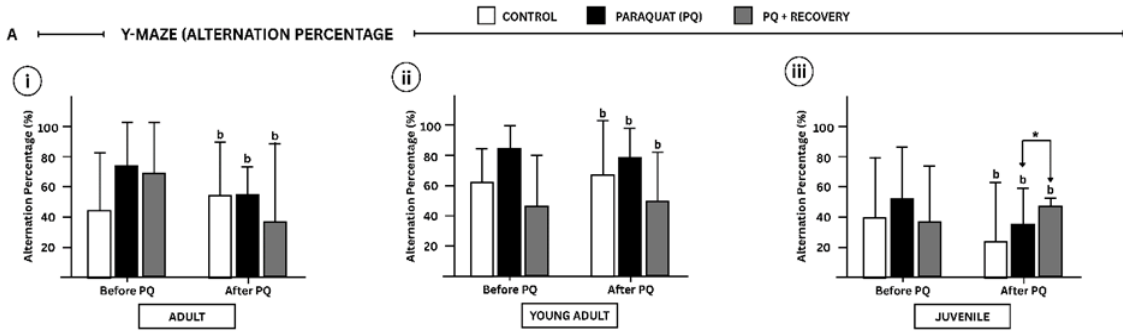

Figure 1: Alternation percentage across all age groups following paraquat treatment and recovery. Data are expressed as mean ± SD. a = significant "pre vs post" differences; b = non-significant "pre vs post" differences. $p \leq 0.05$ considered statistically significant.

Latency-to-Fall

Adult Cohort:

Latency-to-fall did not differ significantly between pre- and post-tests in the control ($p = 0.861$, $d = 0.083$) and paraquat ($p = 0.513$, $d = 0.321$) groups. However, a significant decline was observed in the PQ+Recovery group ($p = 0.050$, $d = 2.305$). ANOVA showed no significant effects of time ($F(1,18) = 1.203$, $p = 0.356$), group ($F(2,18) = 0.803$, $p = 0.431$), or interaction ($F(2,18) = 0.618$, $p = 0.699$). [Figure 2i].

Young-Adult Cohort:

No significant changes in latency-to-fall were found in the control ($p = 0.187$, $d = 0.728$), paraquat ($p = 0.524$, $d = 0.444$), or PQ+Recovery ($p = 0.913$, $d = -0.270$) groups. Time ($F(1,18) = 1.511$, $p = 0.327$), group ($F(2,18) = 1.372$, $p = 0.303$), and interaction effects ($F(2,18) = 1.148$, $p = 0.428$) were all non-significant. [Figure 2ii].

Juvenile Cohort:

No significant within-group differences were observed in latency-to-fall for control ($p = 0.714$, $d = 0.176$), paraquat ($p = 0.863$, $d = -0.083$), or PQ+Recovery ($p = 0.496$, $d = 0.477$) groups. ANOVA revealed no significant effects of time ($F(1,18) = 0.133$, $p = 0.963$), group ($F(2,18) = 3.816$, $p = 0.113$), or interaction ($F(2,18) = 0.790$, $p = 0.594$). [Figure 2iii].

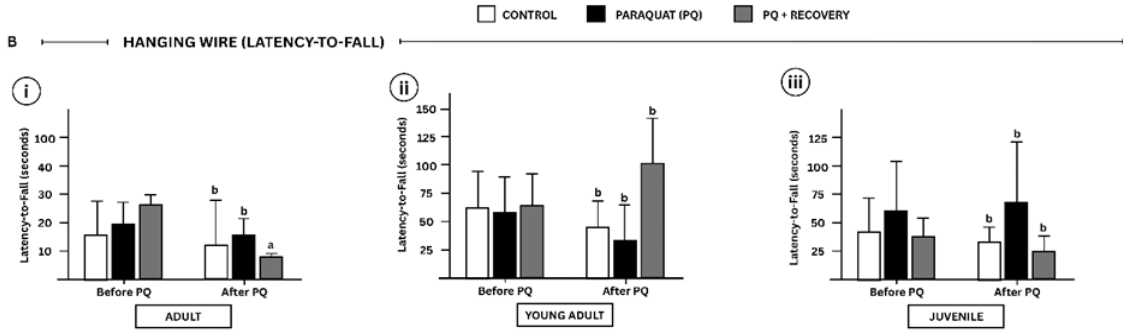

Figure 2: Latency-to-fall (in seconds) across all age groups following paraquat treatment and recovery. Data are Mean ± SD. a = significant "pre vs post" differences; b = non-significant "pre vs post" differences. $p \leq 0.05$ considered statistically significant.

Line Crossings (LC)

Adult Cohort:

A significant reduction in LC was observed in the paraquat group post-treatment ($p = 0.0201$, $R^2 = 0.7779$), indicating decreased locomotor activity. No significant changes were found in the control ($p = 0.8827$, $R^2 = 0.00614$) or PQ+Recovery ($p = 0.5991$, $R^2 = 0.1607$) groups. ANOVA showed no significant effects of time ($F(1,18) = 1.046$, $p = 0.3792$), group ($F(2,18) = 2.464$, $p = 0.0971$), or interaction ($F(2,18) = 0.6221$, $p = 0.7459$). [Figure 3i].

Young-Adult Cohort:

No significant within-group differences were observed in LC for control ($p = 0.5572$, $R^2 = 0.0928$), paraquat ($p = 0.1408$, $R^2 = 0.4564$), or PQ+Recovery ($p = 0.9498$, $R^2 = 0.0156$) groups. Time ($F(1,18) = 1.467$, $p = 0.251$), group ($F(2,18) = 0.759$, $p = 0.491$), and interaction ($F(2,18) = 0.530$, $p = 0.603$) effects were non-significant. [Figure 3ii].

Juvenile Cohort:

LC scores remained unchanged across all groups: control ($p = 0.5480$, $R^2 = 0.0970$), paraquat ($p > 0.9999$, $R^2 \approx 0.0000$), and PQ+Recovery ($p = 0.9797$, $R^2 = 0.0004$). No significant effects of time ($F(1,18) = 0.013$, $p = 0.911$), group ($F(2,18) = 2.557$, $p = 0.127$), or interaction ($F(2,18) = 0.028$, $p = 0.972$) were detected. [Figure 3iii].

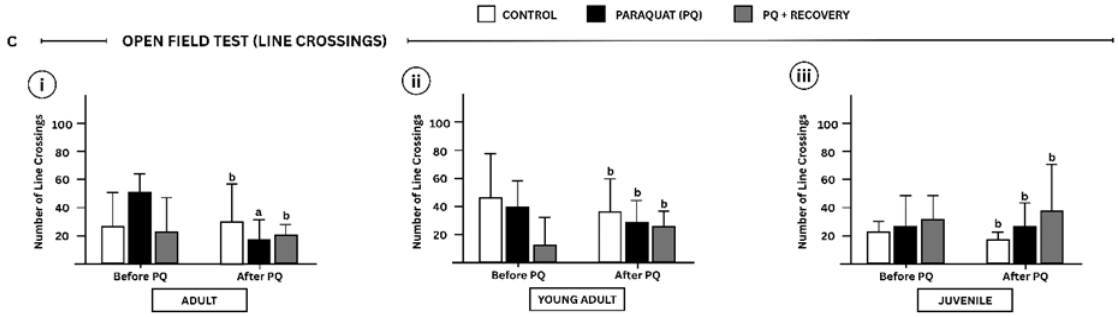

Figure 3: Number of line crossings across all age groups following paraquat treatment and recovery. Data are Mean ± SD. a = significant "pre vs post" differences; b = non-significant "pre vs post" differences. $p \leq 0.05$ considered statistically significant.

Urine Pools (UP)

Adult Cohort:

No significant within-group differences were observed in UP counts for control ($p = 0.059$, $R^2 = 0.632$), paraquat ($p = 0.597$, $R^2 = 0.076$), or PQ+Recovery ($p = 0.189$, $R^2 = 0.659$) groups. However, a significant main effect of time was found ($F(1,18) = 7.857$, $p = 0.019$), suggesting a general shift in urination behavior across testing periods [Figure 4i].

Young-Adult Cohort:

Significant reductions in UP were observed in both the paraquat ($p = 0.0010$, $R^2 = 0.949$) and PQ+Recovery ($p = 0.0016$, $R^2 = 0.976$) groups, while the control group remained stable. ANOVA revealed significant effects of time ($F(1,18) = 36.825$, $p < 0.001$) and group ($F(2,18) = 8.050$, $p = 0.007$), though the interaction was non-significant. Tukey's post-hoc analysis showed that PQ+Recovery animals differed significantly from controls ($p = 0.006$), while the difference between paraquat and recovery groups approached significance ($p = 0.053$). [Figure 4ii].

Juvenile Cohort:

UP counts did not change significantly in the paraquat ($p = 0.704$, $R^2 = 0.040$) or PQ+Recovery ($p = 0.225$, $R^2 = 0.600$) groups. However, the control group exhibited a significant decrease ($p = 0.0061$, $R^2 = 0.877$). Significant main effects of time ($F(1,18) = 11.214$, $p = 0.007$), group ($F(2,18) = 4.209$, $p = 0.047$), and their interaction ($F(2,18) = 4.590$, $p = 0.039$) were observed. Post-hoc comparisons indicated that recovery animals had significantly lower urination than controls ($p = 0.050$), while paraquat vs. control differences were non-significant ($p > 0.9$). [Figure 4iii].

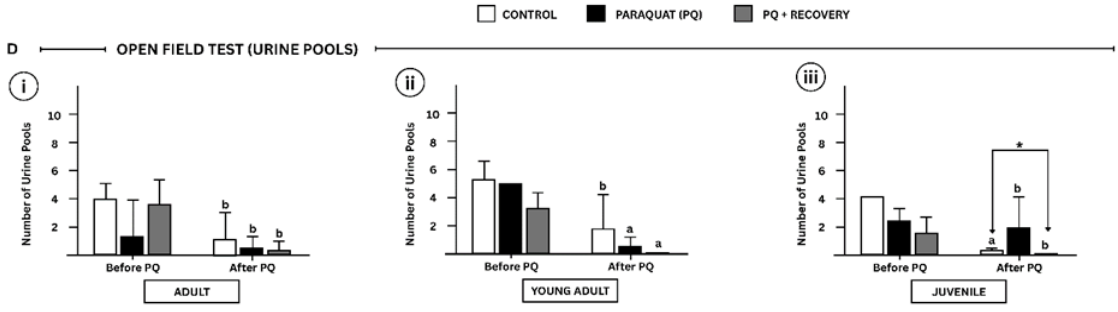

Figure 4: Number of urine pools across all age groups following paraquat treatment and recovery. Data are Mean ± SD. a = significant "pre vs post" differences; b = non-significant "pre vs post" differences. $p \leq 0.05$ considered statistically significant.

Discussion

This study examined the age-dependent effects of paraquat-induced Parkinsonism on neurobehaviour in male Wistar rats by assessing motor, cognitive, and autonomic-related behaviours across juvenile, young-adult, and adult cohorts. Paraquat was administered intraperitoneally at 10 mg/kg twice weekly for three weeks, followed by a two-month recovery phase to evaluate the persistence or reversibility of behavioural changes. The findings reveal that paraquat exposure produces distinct neurobehavioural outcomes that vary with age, underscoring the importance of developmental stage in modulating susceptibility to environmental neurotoxins.

Adult rats exhibited the most pronounced motor impairments, particularly in the hanging wire test, indicating compromised neuromuscular coordination and endurance. These deficits are consistent with the known vulnerability of mature dopaminergic systems to oxidative stress and mitochondrial dysfunction, hallmark mechanisms of paraquat toxicity [18,21,26,27,28,29,30]. The observed decline in exploratory behaviour, as evidenced by reduced line crossings in the open field test, further supports the presence of motor hypoactivity in adult animals, aligning with previous reports of paraquat-induced Parkinsonian-like symptoms in rodents.

In contrast, juvenile and young-adult rats demonstrated relative preservation of motor and cognitive function, as reflected by stable performance in the hanging wire and Y-maze tests. This suggests that younger animals may possess neuroprotective advantages, such as enhanced synaptic plasticity, more robust antioxidant defenses, or greater redundancy in developing neural circuits. These compensatory mechanisms may buffer against the immediate behavioural consequences of paraquat exposure, delaying the onset of overt dysfunction.

Interestingly, despite the absence of significant motor or cognitive impairments, younger cohorts displayed alterations in urination behaviour, particularly in the open field test. Micturition is regulated by complex neural circuits involving the cortex, brainstem, and autonomic pathways [31]. Disruption in this domain may reflect early-stage neurobehavioural dysregulation, potentially serving as a sensitive indicator of sub-clinical neurotoxicity. This finding is particularly relevant to Parkinson's disease, where non-motor symptoms such as autonomic dysfunction often precede classical motor manifestations [32].

The age-dependent pattern of neurobehavioural effects observed in this study is consistent with findings by Thiruchelvam et al., [33] who reported increased behavioural vulnerability to paraquat in older animals. The relative resistance of juvenile and young-adult rats supports the hypothesis that early-life exposures may result in latent or subthreshold behavioural changes that could emerge or intensify with age or subsequent neurotoxic challenges. This has important translational implications, suggesting that behavioural compensation in younger individuals may mask early signs of neurodegeneration, complicating timely diagnosis and intervention.

Following the recovery period, partial behavioural stabilization was observed, particularly in younger cohorts, indicating some capacity for functional recovery. However, persistent motor deficits in adult rats suggest that once age-related vulnerability is established, behavioural impairments may be less reversible. This mirrors clinical patterns in neurodegenerative diseases, where ageing diminishes the brain's ability to compensate for neuronal loss or damage [34].

Mechanistically, paraquat exerts its neurotoxic effects through the generation of reactive oxygen species, mitochondrial impairment, and oxidative stress, processes that disproportionately affect dopaminergic neurons and their associated behavioural output [18,29]. While histological confirmation was beyond the scope of this study, the behavioural data alone underscore the sensitivity of neurobehavioural assays in detecting early functional impairments. Additionally, genetic and strain-specific factors may influence behavioural outcomes, as demonstrated by Jiao et al. [35], and should be considered in future investigations.

Conclusion

In conclusion, this study highlights the critical role of age in shaping neurobehavioural responses to paraquat-induced Parkinsonism. The findings emphasize that neurobehavioural assessments; particularly those targeting both motor and non-motor domains, are essential for early detection of toxicant-induced dysfunction. Longitudinal behavioural profiling across developmental stages may enhance our understanding of environmental contributions to neurodegenerative disease risk and progression.

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