Title: Transversal investigation of apathic behaviors in a Parkinson's disease mouse model with 6-hydroxydopamine lesioning in the bilateral dorsal striatum

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Background: Parkinson's disease (PD) is associated with various non-motor symptoms. Among these, apathy consists of many symptoms related to emotional, self-care, and social interaction behaviors. Apathy has great impact on the lives of PD patients; however, its detailed pathology remains unknown.

Aims & Objectives: We transversally investigated each domain of apathic behaviors in PD mouse model with 6-hydroxydopamine (6-OHDA), which induces dopamine neuronal death, an intrinsic pathological change of PD, lesioned in the bilateral dorsal striatum.

Methods: We allocated 8-week-old male C57/BL6J wild-type mice (n=21) to either the 6-OHDA (n=13) or sham (n=8) groups. The 6-OHDA group received bilateral administration of 4 μg/1 μL of 6-OHDA dissolved in 0.25% ascorbic acid (AA) in saline, while the sham group received 1 μL of 0.25% AA in saline alone, both into the dorsal striatum. Before 6-OHDA lesioning and 3 weeks after that, we conducted rotarod, pole, and balance beam tests to evaluate motor function decline reflecting the PD model. After the motor performance tests, the sucrose preference test (SPT) and novelty-suppressed feeding test (NSFT) were used to assess anhedonia, the nest-building test (NBT) and splash test were used to assess self-grooming, the open-field test (OFT) and hole-board test (HBT) were used to assess anxiety and explore behavioral aspects, and the three-chamber social test was used to assess social interaction behavior. After the experiment, pathological evaluation with tyrosine hydroxylase (TH) immunostaining of the substantia nigra (SN) and ventral tegmental area (VTA) was performed and analyzed using the ImageJ software.

Results: One mouse from the 6-OHDA group died postoperatively. At 3 weeks after 6-OHDA lesioning, the 6-OHDA group exhibited significant impairments in the rotarod test (before lesioning: 221.5 [mean]±74.4 [SD] s; after lesioning: 150.6±49.8 s; $P<0.001$), pole test Tdown (total time taken to turn and descend the pole; before: 9.0±1.5 s; after: 10.1±1.7 s; $P<0.05$), and balance beam test (before: 8.7±1.9 s; after: 11.7±2.7 s; $P<0.05$). In contrast, motor function test results in the sham group did not change significantly after vehicle administration. In apathic behavioral tests, a significant difference was observed in the score of NBT (6-OHDA group:1.4±0.6 vs. sham group: 2.1±0.8; $P<0.05$), the latency time to eat food in NSFT (254.8±93.2 s vs. 159.1±91.7 s; $P<0.05$), the latency time to first grooming

in splash test (6.4±4.5 s vs. 3.0±1.1 s; $P<0.05$) and the head dip counts in HBT (10.0±5.0 vs. 16.6±5.5; $P<0.05$), respectively. In pathological evaluation, the number of TH+ pixels in SN and VTA were significantly reduced in 6-OHDA group compared to the sham group (SN: 10.4±1.9 vs. 13.2±3.2; $P<0.05$; VTA: 11.2±1.9 vs. 13.3±2.3; $P<0.05$).

Discussion & Conclusion: In the present study, a PD mouse model with relatively localized dopaminergic neuronal loss in the dorsal striatum was generated. Among the multiple domains of symptoms with apathy, this PD mouse model expresses impaired self-care and novelty seeking behavior.