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ORIGINAL ARTICLE

Ventral striatal dopaminergic loss drives dopamine dysregulation syndrome-like behaviors in an experimental model of parkinsonism

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ABSTRACT

Objectives: This study aimed to establish an animal model to investigate the pathophysiology of these behaviors and to explore the role of ventral versus dorsal distribution of dopaminergic denervation.

Materials and methods: This experimental study was conducted with 70 male Sprague-Dawley rats (mean weight: 358±43 g). A low dose of 6-hydroxydopamine (6-OHDA) or 0.9% saline was bilaterally injected into either the ventral tegmental area or the substantia nigra. Additionally, a control group of intact rats was included. The rewarding properties of apomorphine were assessed using the conditioned place preference paradigm. Stereotypical and dyskinetic behaviors were induced by daily high-dose apomorphine treatment and evaluated using two behavioral scales. At the end of the experiments, the extent of dopaminergic denervation was confirmed by tyrosine hydroxylase immunohistochemical staining.

Results: All rats with dopaminergic lesions developed dyskinetic behaviors following apomorphine administration. The severity of these behaviors increased progressively and was strongly correlated with the mean lesion volume ($r=0.849$, $p<0.001$). Low-dose apomorphine induced conditioned place preference in parkinsonian rats but conditioned place avoidance in control animals. The conditioning score was higher in the ventral-dominant denervation group and moderately correlated with the mean ventral lesion volume ($r=0.642$, $p=0.001$).

Conclusion: These findings suggest that the rewarding effects of dopamine replacement therapy are associated with the sensitization of the ventral striatum due to dopaminergic denervation.

Keywords: Dopamine dysregulation syndrome, punding, substansia nigra, ventral tegmental area, 6-hydroxydopamine.

Parkinson disease (PD) is a common progressive neurodegenerative disease.[1] While dopaminergic drugs and surgical methods are effective for managing motor symptoms, the hallmark of PD, these approaches are often insufficient in the advanced stages of the disease, particularly for nonmotor symptoms.[2] In recent years, awareness has grown regarding dopamine replacement therapy (DRT)-induced impulse control and related behavioral disorders,[3-5] which include impulse control disorders, punding, and dopamine dysregulation syndrome (DDS). In this study, we focused on punding and DDS.

Punding refers to complex, purposeless, repetitive behaviors and was initially observed in individuals with amphetamine addiction.[3] In PD, punding is most often associated with DRT, with a prevalence ranging from 1.4 to 14%.[6,7] While nearly all patients eventually develop dyskinesias during long-term DRT, only a minority exhibit punding, suggesting a different underlying mechanism. Imaging and pathological studies indicate that

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variation in ventral striatal denervation may contribute to this discrepancy.[8,9]

Dopamine dysregulation syndrome resembles drug addiction, where patients compulsively use dopaminergic medication at harmful doses. It is typically associated with high-potency, fast-acting dopamine agonists such as apomorphine.[10] The prevalence is estimated to be between 3.4 and 4.1% among PD patients.[10,11] Imaging studies have linked DDS to enhanced dopamine release in the ventral striatum.[12,13] Various lesion models have been used to replicate these effects in animals.[14-17]

This study aimed to compare the behavioral and neurochemical outcomes of dorsal versus ventral-predominant striatal dopaminergic denervation. We employed bilateral partial 6-hydroxydopamine (6-OHDA) lesions targeted to either the substantia nigra (SN) or the ventral tegmental area (VTA), followed by chronic apomorphine treatment. Our objective was to evaluate differences in the development of DDS- and punding-like behaviors and to establish a model that avoids severe motor deficits, which often confound behavioral assessments in existing bilateral lesion paradigms.

MATERIALS AND METHODS

Seventy male, Sprague-Dawley rats (mean weight: 358±43 g) were used in this study. All animals were kept at constant humidity, at room temperature (18-20°C), and on a 12-h light-dark cycle throughout the entire study. Food and drink restrictions were not made. Rats were randomly divided into five different groups: 6-OHDA injected into *(i)* VTA or *(ii)* SN, 0.9% saline injected into *(iii)* VTA or *(iv)* SN, and *(v)* intact rats to create partial dopaminergic denervation in the striatum at different topographic extensions. The animals were assigned to VTA and SN groups after validating the dopaminergic denervation extension with staining. Six animals were excluded from the study because of inconclusive staining. The study protocol was approved by the Hacettepe University Animal Experiments Local Ethics Committee University Animal Experiments Ethics Committee (Date: 14.04.2015, No: 2015/29-01).

Surgical procedures

Rats were anesthetized with intraperitoneal injections of ketamine (50 mg/kg) and xylazine (8 mg/kg) and placed in a stereotaxic frame. Ten micrograms of 6-OHDA hydrobromide (Sigma-Aldrich, St. Louis, MO, USA), dissolved in 5 µL of 0.9% with 0.02% ascorbic acid (w/v), was infused at a rate of 1 µL/min, and the needle was left in the same position after injections for an additional 3 min to give time for adequate diffusion of 6-OHDA to the region of interest. Twenty-one rats received bilateral stereotaxic 6-OHDA injection targeted to SN according to Pellegrino rat brain atlas at coordinates 5.2 mm posterior and 2 mm lateral to bregma, 7.2 mm ventral to dural surface, and tooth bar 2.3 mm below the interaural line. Ventral segmental area coordinates were 6 mm posterior and 1 mm lateral to bregma, 8 mm ventral to the dural surface, and the tooth bar was left at the neutral position for 17 rats. Sham-operated rats (n=10 for SN, n=10 for VTA) underwent the same surgical procedures but only received 5 µL of 0.9% saline, and intact rats (n=6) did not undergo any surgical procedure. After surgical procedures were completed, a three-week interval was given before starting the behavioral experiments.

Behavioral experiments

To determine the extent of motor disturbances based on bilateral dopaminergic neuronal loss, an open-field test was used. The rats were placed in an activity cage (45×45×30 cm) and analyzed for basal motor activity for 1 h. After the experiment, the total distance traveled was evaluated using Ethovision XT video tracking software (14th version, Noldus, Wageningen, Netherlands).

For CPP, a three-chambered box separated by guillotine doors, which has two identical end chambers (15×15×20 cm) and a central chamber (5×15×20 cm), was used. The end chambers were arranged differently for visual and tactile cues as wall paintings (mottled or striped) and floor properties (holes 4 mm or 4 cm in diameter). At the pretest, while the doors of the CPP box were open, rats were allowed to spend 15 min of free time. The time spent at each chamber was noted. The end chamber, which the rat spent less time in at the pretest associated with apomorphine injection. At conditioning days, rats received either 0.1 mg/kg of apomorphine (Britannia Pharmaceuticals-Gen Drugs, London, UK) or the same volume of saline intraperitoneally and were placed immediately in the chamber assigned while the guillotine doors closed. All rats had eight conditioning sessions, each lasting 30 min, and an apomorphine day followed by a saline day. On the test day after conditioning, the rats were allowed to spend 15 min of free time with the entire apparatus. At the end of the experiment, the conditioning score (CS) was

calculated in seconds as the time spent on the test day at drug-associated chamber minus the time spent there during the pretest. Positive and negative scores were considered CPP and conditioned place avoidance, respectively.

After the CPP experiment, rats were divided into two groups and given daily apomorphine 1 mg/kg (n=45) or saline treatment (n=19). After seven days of treatment, a last challenge dose was given after a week of drug-free interval. For all treatment days, rats were videotaped at the 20th and 50th min after injections. These videos were then analyzed by an investigator blind to treatment groups.

Dyskinesias were analyzed with a scale adapted for bilateral models.[18] In this scale, dyskinesias were classified into four types: locomotive dyskinesias, axial dystonia, orolingual dyskinesias, and right and left forelimb dyskinesias. Each of these four types was scored from 0 (absent) to 4 (severe), giving a total score between 0 and 20 (for the limb dyskinesias, the right and left sides were scored separately). Stereotypic behavior was analyzed by the classical stereotypy scale.[19] Animals were rated as follows: 0=asleep or stationary; 1=active; 2=mostly active with a burst of rearing or sniffing; 3=sniffing along the same patch of the cage; 4=sniffing on the same cage spot; 5=stereotypic plus burst of licking; 6=continuous licking or gnawing at the same location. Stereotypy scores were calculated as the sum of the 20- and 50-min values for the day. The timeline of the study is shown in Figure 1.

Perfusion and staining

At the end of experiments, 2 to 4 h after the last injections, all animals were decapitated after high-dose chloralhydrate anesthesia, followed by intracardiac perfusion with a 4% paraformaldehyde solution in 0.1 M phosphate buffer. Brains were extracted and maintained for one day at room temperature in perfusion solution (4% paraformaldehyde) and then 30% glucose solution at +4°C for at least 24 h for cryoprotection. Fresh-frozen coronal brain sections 20 µm in thickness, which were acquired with a microtome (Leica CM 1100; Leica Microsystems, Wetzlar, Germany), were placed on poly-L-lysine-covered slides and dried in air to fix.

One section per 200 µm of the striatum was selected for staining. The staining protocol was explained in detail elsewhere.[20] Before the staining protocol, for antigen retrieval, the sections were subjected to a solution containing 0.05% trypsin and 0.1% calcium chloride for 30 min at 37°C. After washing twice with phosphate-buffered saline (PBS), slides were left in hydrogen peroxide blocking solution (IHC kit, ab80436; Abcam Limited, Cambridge, UK) for 10 min. Again, slides were washed with PBS , and protein blocking solution (ab80436) was put on slides for another 10 min. After blocking finished, a 1:1000 concentration of anti-tyrosine hydroxylase antibody (EP1533Y; Abcam Limited, Cambridge, UK) in PBS-covered sections was kept at +4°C overnight. The next day, the complement solution (ab80436) for 10 min, then HRP conjugate (ab80436) for 15 min was applied to the section. Lastly, a 1:50 concentration of DAB chromogen (ab80436) in DAB substrate (ab80436) was put on slides until a brownish color emerged. After the protocol had finished, the slides were examined by a camera-embedded light microscope (Eclipse E600, Ex 450-560 nm;

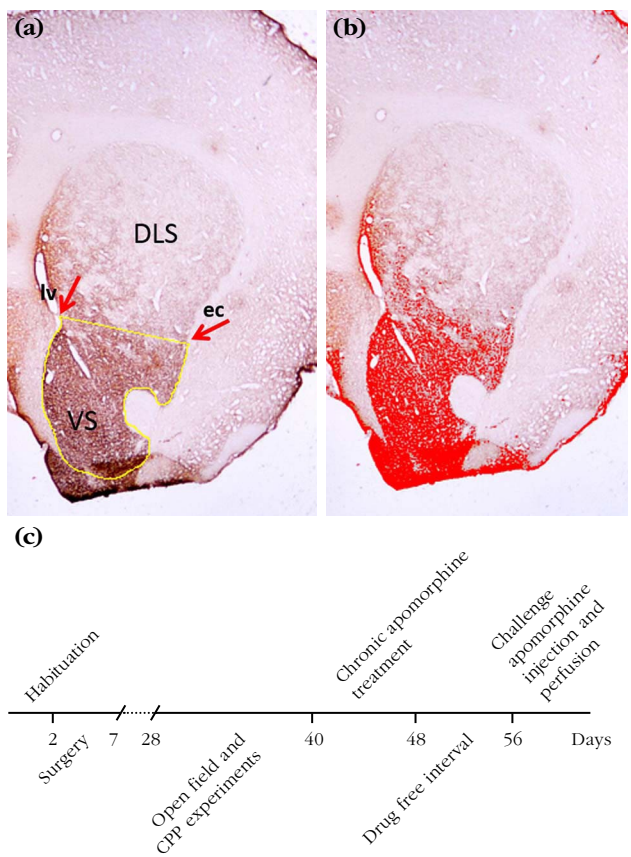

Figure 1. Image analysis and study timeline. **(a)** The border between the VS and DLS is defined by a line connecting the ec and the lv. **(b)** An example of thresholding performed using ImageJ software. **(c)** Timeline of the study.
CPP: Conditioned place preference; DLS: Dorsolateral striatum; VS: Ventral striatum; lv: Lateral ventricle; ec: External capsule.

Nikon Eclipse Ci-E, Tokyo, Japan) and pictures of sections were captured at ×10 magnification with the NIS-Elements AR version 2.30 software (Nikon Eclipse Ci-E, Tokyo, Japan).

Sections of the striatum that were 1.7, 1.2, and 0.7 mm anterior to the bregma were selected for evaluation of dopaminergic denervation. For each brain, the lesion area and total striatal area were calculated with an image processing program (ImageJ 1.50i; National Institutes of Health, Bethesda, Maryland, USA) at these three coordinates, and an average of these values was used to calculate the mean lesion volume. To determine the dorsal and ventral extent of the lesion, the line that combines the most ventral edge of the lateral ventricle and external capsule was accepted as a border. The lesions dorsal to the line were accepted as dorsal lesions, and ventral ones as ventral lesions. For each subject, the mean dorsal and ventral lesion volumes were calculated (Figure 1).

Statistical analysis

All statistical analyses were performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). All data were shown as mean ± standard deviation (SD). Normality assumptions were made by the Shapiro-Wilk normality test. Group comparisons were done by the one-way analysis of variance (parametric data) or Kruskal-Wallis tests (nonparametric data). Tukey's honestly significant difference or Dunn's multiple comparisons tests were used for post hoc analyses. Changes in dyskinesia and stereotypy scores by treatment days were analyzed by the repeated measures analysis of variance. The relation between striatal lesion percentages and behavioral parameters was examined using the Pearson correlation coefficient.

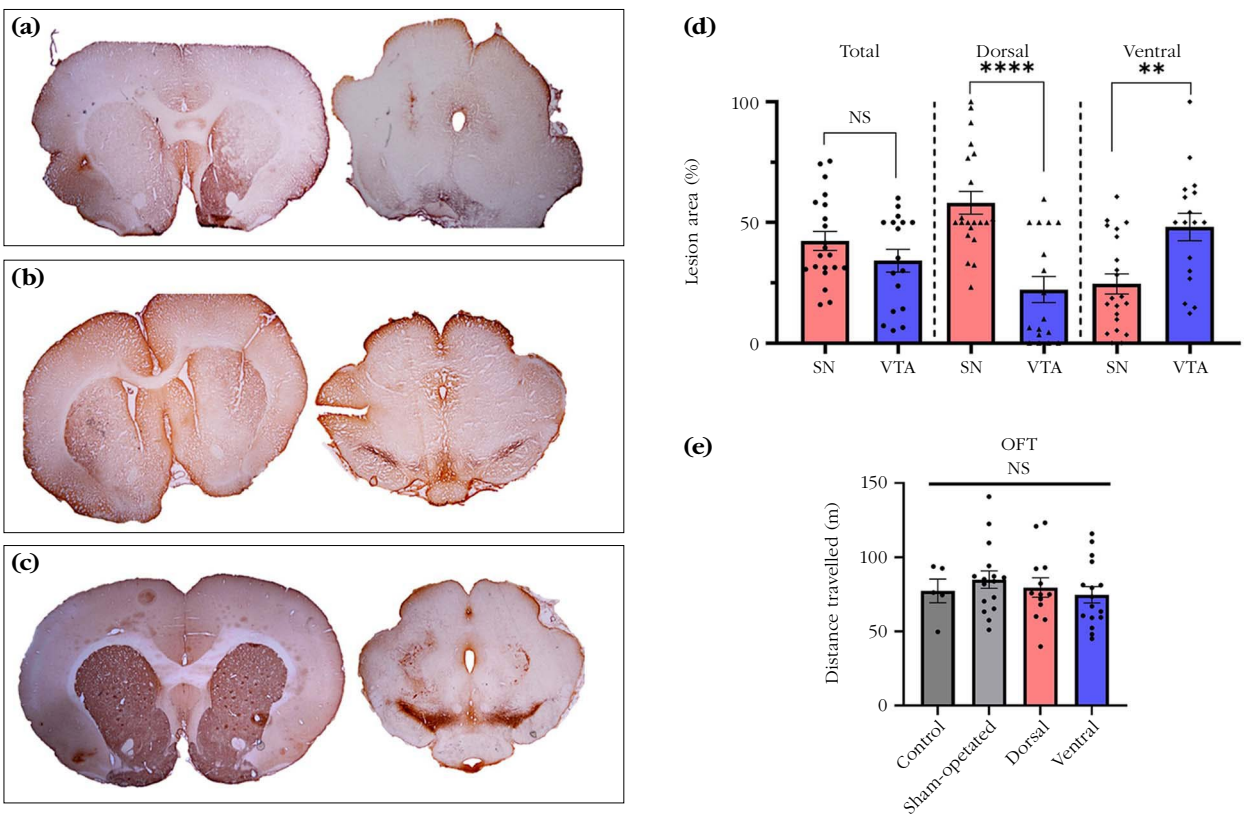

Figure 2. Extent of dopaminergic lesion and locomotor activity. **(a-c)** Representative coronal brain sections stained for tyrosine hydroxylase at the levels of the striatum and SN are shown for the SN **(a)**, VTA **(b)**, and control **(c)** groups. **(d)** Quantification of the percentage area of dopaminergic denervation. Total striatal lesion extent was similar between groups. However, the SN group showed significantly greater denervation in the dorsal striatum ($p<0.001$) and less denervation in the ventral striatum compared to the VTA group ($p=0.002$). **(e)** Total distance traveled in the OFT was comparable across all groups.

NS: Not significant; SN: Substantia nigra; VTA: Ventral tegmental area; OFT: Open field test.

The level of statistical significance was accepted as $p<0.05$.

RESULTS

The bilateral 6-OHDA toxin models can lead to mortality rates of up to 82%.[21] Because of severe adipsia and aphagia, animals sometimes need tube feeding for survival. Although unilateral models are more compatible with survival, postural biases, particularly ipsilateral rotation induced by apomorphine, can cause misinterpretation of the behavioral test results.

For the VTA group (n=17), the mean total striatal lesion percentage was 34±3.23, the mean ventral striatal lesion percentage was 48±2.09, and the mean dorsal striatal lesion percentage was 22±4.78. For the SN group (n=21), the mean total striatal lesion percentage was 42±4.43, the mean ventral striatal lesion percentage was 24±5.89, and the mean dorsal striatal lesion percentage was 58±1.23. The dorsal lesion percentage in the SN group was significantly higher than the VTA group ($p<0.001$), and the ventral lesion percentage in the VTA group was significantly higher than the SN group ($p=0.002$). Total striatal lesion volume was similar in VTA and SN groups ($p=0.185$). Sham-operated subjects and controls did not show dopaminergic denervation. Representative pictures and striatal lesion percentages are shown in Figure 2.

After surgical procedures, all animals survived and continued with further experiments. Severe weight loss was not detected. The mean weight of the animals was 358±43 g, which showed no significant difference between the groups ($p=0.595$). Basic motor abilities were studied with open-field locomotor activity tests. The total distance traveled in the open field test was comparable across all groups ($p=0.535$). This finding supports that partial dopaminergic denervation does not cause severe bradykinesia.

The mean CS was 172±214 in the ventral weighted lesion group, 99±202 in the dorsal weighted lesion group, –32±92 in the sham-operated group, and –62±60 in the controls. The CS showed a significant difference between groups (Kruskal-Wallis test, $H(4.62)=21.95$; $p<0.001$). The SN group showed significantly higher CS scores than both the control ($p=0.045$) and sham-operated ($p=0.025$) groups. The VTA group also had significantly higher CS scores compared to the control and sham groups ($p=0.004$, $p=0.001$, respectively). The VTA group tended to have higher CS scores than the SN group, but this difference did not reach statistical significance (Figure 3a). Furthermore, we analyzed the correlation between lesion volumes and CS; the mean ventral lesion percentages were positively correlated with CS (Pearson test, $r=0.642$; $p<0.001$; Figure 3b).

Dyskinetic behaviors developed and increased significantly day by day during treatment in all denervated subjects that received apomorphine for treatment ($n=28$, $p<0.001$). In addition, it was observed that after a one-week drug-free interval following the treatment period, a challenge dose of apomorphine induced dyskinetic behaviors close to the last day of treatment. This is explained by behavioral sensitization. Dyskinesia scores according to the treatment days are shown in Figure 3c. Sham-operated rats, controls, and the denervated rats treated with SF did not develop dyskinetic behaviors.

Dyskinesia scores that were compared for each day of treatment separately did not show significant differences between SN and VTA groups (first day, $p=0.548$; challenge day, $p=0.292$). In parallel with our findings, patients with PD suffer from dyskinetic behaviors as DRT duration gets longer. Additionally, being at a late stage of the disease (more severe dopaminergic denervation) is a risk factor for developing dyskinesias. When the relationship between the dyskinetic behaviors (last day's dyskinesia scores) and the weight of the dopaminergic denervation was investigated in our data, it was found that the mean lesion percentage and the dyskinesia score were strongly and positively correlated (Pearson test, $r=0.849$; $p<0.001$).

All rats treated with apomorphine, including the sham-operated rats and controls, developed stereotypic behavior ($n=45$). Stereotypies did not show a gradual increase with treatment days as in dyskinesia. Instead, the score increased initially and then stayed at a similar level (Figure 3d). Dyskinesia scores on the first and the last treatment days between groups and change of scores with time did not show a significant difference (first day between groups, $F=0.983$, $p=0.411$; seventh day between groups, $F=1.153$, $p=0.340$; change by day, $p=0.453$). In addition, after challenge apomorphine injection, stereotypies were more pronounced in sham-operated animals and controls. For challenge day, stereotypy scores showed a significant difference between groups ($F=9.625$, $p<0.001$). Post hoc analysis pointed out that SN group stereotypy

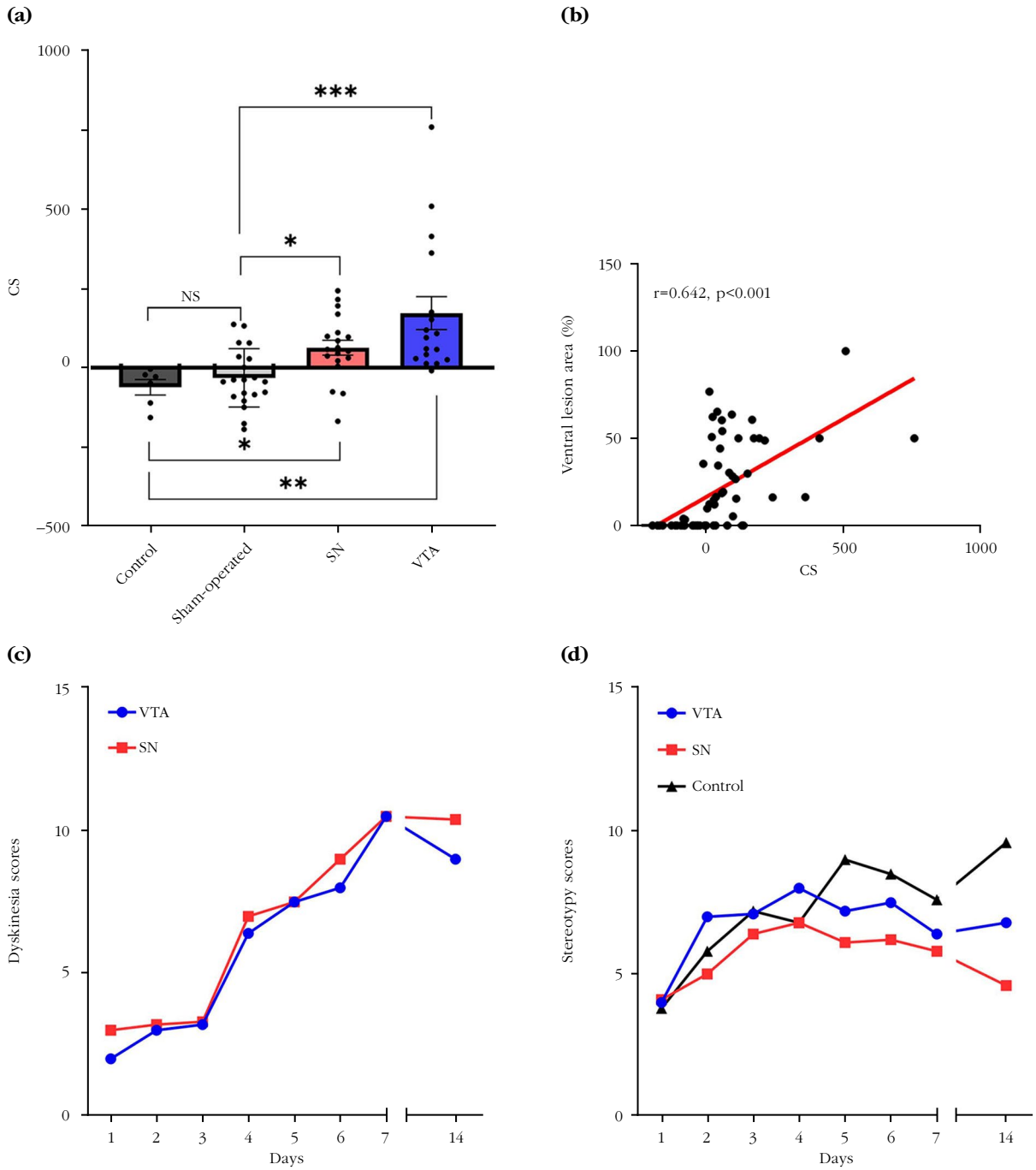

Figure 3. Conditioning scores and behavioral scale results. **(a)** Conditioning scores were similar between the control and sham-operated groups. The SN group showed significantly higher CS scores than both the control (p=0.045) and sham-operated (p=0.025) groups. The VTA group also had significantly higher CS scores compared to the control and sham groups (p=0.004 and p=0.001, respectively). The VTA group tended to have higher CS scores than the SN group, but this difference did not reach statistical significance. **(b)** A moderate positive correlation was observed between the percentage of ventral striatal lesion and the CS scores. **(c)** Dyskinesia scores gradually increased and remained elevated following a seven-day drug-free interval in both SN and VTA groups. Control animals exhibited no dyskinesia. **(d)** Stereotypy scores increased progressively and reached a plateau in all groups. Interestingly, control animals showed significantly higher sensitization after the drug-free interval compared to the other groups.

CS: Conditioning score; NS: Not significant; SN: Substantia nigra; VTA: Ventral tegmental area.

scores were significantly lower compared to sham-operated rats and controls ($p<0.001$ and $p=0.003$; respectively).

DISCUSSION

In this study, we investigated the differential effects of ventral versus dorsal-predominant dopaminergic denervation. Importantly, we successfully established a targeted partial denervation model that did not result in significant locomotor deficits or weight loss. The group with VTA lesions exhibited higher conditioning scores, which positively correlated with the severity of ventral striatal dopaminergic denervation. While dyskinetic behaviors were associated with the extent of dopaminergic denervation, stereotypic behaviors were observed even in control animals treated with apomorphine. Interestingly, these control animals showed greater drug sensitization over time.

Locomotor activity was assessed using the open-field test, and no significant differences were found between groups. This aligns with the understanding that motor symptoms in PD typically emerge after more than 80% of dopaminergic neurons in the SN are lost. In our study, none of the animals exhibited bilateral striatal denervation exceeding this threshold. Similarly, a previous study using bilateral partial lesions in the medial VTA and SN pars compacta induced with 6-OHDA also reported no locomotor deficits compared to controls.[22] To capture more subtle motor impairments in future studies, more sensitive tests such as the stepping test may be employed to assess fine motor control.

Dopamine dysregulation syndrome is thought to be due to a sensitization in the ventral striatum. In imaging studies, it was found that levodopa-related dopamine release was greater in patients with DDS than in those without DDS.[12] For the DDS animal model, the conditioned place preference paradigm has been used so far by several studies.[14-17] Parallel with the imaging results, bilateral nucleus accumbens (NAc) denervation was performed by bilateral posterior VTA 6-OHDA injection, and denervated animals showed CPP with D2 and D3 agonists but not with cocaine.[13] In addition, a different study showed that pramipexole in a bilateral 6-OHDA-induced striatal lesion model and D2 and D3 agonists in a 6-OHDA-induced bilateral medial forebrain bundle model triggered CPP.[15,16] Lastly, the unilateral denervation model by 6-OHDA injection to the medial forebrain bundle demonstrated that D1/D2 agonist apomorphine was rewarding at low doses for denervated animals.[17]

Our findings support the notion that DDS in PD is associated with the severity of ventral striatal dopaminergic denervation. Additionally, recent imaging studies in patients with PD demonstrated that VTA dopaminergic neuron loss was more variable than that in the SN,[8] with postmortem studies showing interindividual variability in VTA denervation ranging from 40 to 77%.[9] This variability may help explain why DDS does not develop in all patients, unlike dyskinesia, which is more consistently observed.

Spine enlargement of medium spiny neurons (MSNs) is considered a key pathological feature of levodopa-induced dyskinesia. Interestingly, in a rat model of levodopa-induced dyskinesia, similar spine enlargement was observed in MSNs of the NAc.[23] This excitatory supersensitivity of NAc MSNs may contribute to the development of DDS.

Stereotypy is described as abnormal timing or release of ordinary movements and is usually repetitive and aimless.[24] Punding is thought to be similar to stereotypical movements that have been studied in animal models for many years. Our clinical knowledge about PD suggests that D2/D3 receptor agonists rarely lead to the development of punding.[25] Therefore, in our study, we used D1/D2 receptor agonist apomorphine at a high dose (1 mg/kg) for chronic treatment to induce stereotypic and dyskinetic movements.

All apomorphine-treated rats in our study developed stereotypic behaviors, supporting the idea that such behaviors, commonly considered models of punding, can occur independently of dopaminergic denervation. This is consistent with clinical observations, where punding has been reported in diseases treated with dopamine agonists, even in the absence of dopaminergic cell loss, such as prolactinomas and restless legs syndrome.[26]

Previous studies reported a positive correlation between the severity of punding and dyskinesias in patients with PD.[24,26] To our knowledge, this is the first study to investigate apomorphine-induced CPP in a bilateral PD model comparing ventral- and dorsal-weighted patterns of dopaminergic denervation.

In summary, our results indicated that DDS was associated with ventral striatal denervation

severity, while dyskinesia correlated with both the extent of dopaminergic denervation and the duration of treatment. Stereotypic behaviors, however, were less clearly linked to denervation and may be influenced more by dopamine agonist exposure itself. Interestingly, stereotypy scores were lower in rats with dorsal-predominant lesions, which may reflect limitations of current rating scales in capturing the rich and complex behavioral repertoire in denervated animals. Therefore, future studies would benefit from the development of a revised behavioral scale that can clearly differentiate between dyskinetic and stereotypic movements to better understand the behavioral consequences of dopaminergic denervation.

This study contributes to the understanding of how different topographies of dopaminergic denervation in the striatum affect the emergence of behavioral complications related to DRT in PD. By establishing a bilateral, partial denervation model with preserved motor function, we demonstrated that ventral striatal denervation was specifically linked to DDS-like behavior, while stereotypic (punding-like) behaviors appeared to be more directly induced by dopamine agonist treatment. These findings provide a refined model for investigating impulse control and related behavioral disorders in PD and highlight the importance of considering ventral striatal integrity in both research and clinical contexts.

This study has some limitations. First, the extent of dopaminergic denervation was not strictly confined to either the ventral or dorsal region, as each animal showed some degree of crossover between two. Second, the dyskinesia scales used to assess motor complications in the model were limited in their ability to capture the full range of behavioral outcomes in denervated animals.

In conclusion, this study highlighted a potential link between the severity of ventral striatal dopaminergic denervation and the development of DDS in PD. Previous imaging studies revealed that ventral dopaminergic neuron loss was highly variable among PD patients. With the advancement of neuroimaging techniques, it may soon be possible to directly assess VTA neuron loss in vivo, allowing for the identification of individuals at greater risk of developing DDS. Additionally, all rats treated with dopamine agonists exhibited stereotyped behaviors, indicating that punding may be a common side effect of such therapies. These findings support the inclusion of routine screening for punding symptoms in the clinical management of PD.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Designed the study, conducted all experiments, analyzed the data, and wrote the manuscript: E.O.; Helped with the design and the experiments: G.Y.C., Ö.Ö.Ç.; Supervised the study: E.S.T. All authors have read and accepted the final version of the manuscript.

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