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Pramipexole-induced impulsivity in mildparkinsonian rats: a model of impulse control disorders in Parkinson's disease

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ABSTRACT

Treatment with dopaminergic agonists such as pramipexole (PPX) contributes to the development of impulse control disorders (ICDs) in patients with Parkinson's disease (PD). As such, animal models of abnormal impulse control in PD are needed to better study the pathophysiology of these behaviors. Thus, we investigated impulsivity and related behaviors using the 5-choice serial reaction time task, as well as FosB/ΔFosB expression, in rats with mild parkinsonism induced by viral-mediated substantia nigra overexpression of human A53T mutated α-synuclein, and following chronic PPX treatment (0.25 mg/kg/d) for 4 weeks. The bilateral loss of striatal dopamine transporters (64%) increased the premature response rate of these rats, indicating enhanced waiting impulsivity. This behavior persisted in the OFF state after the second week of PPX treatment and it was further exacerbated in the ON state throughout the treatment period. The enhanced rate of premature responses following dopaminergic denervation was positively correlated with the premature response rate following PPX treatment (both in the ON and OFF states). Moreover, the striatal dopaminergic deficit was negatively correlated with the premature response rate at all times (pretreatment, ON and OFF states) and it was positively correlated with the striatal FosB/ΔFosB expression. By contrast, PPX treatment was not associated with changes in compulsivity (perseverative responses rate). This model recapitulates some features of PD with ICD, namely the dopaminergic deficit of early PD and the impulsivity traits provoked by dopaminergic loss in association with PPX treatment, making this model a useful tool to study the pathophysiology of ICDs.

1. Introduction

Dopaminergic therapy in Parkinson's disease (PD) is associated with the development of impulse control disorders ([ICDs] compulsive gambling, shopping, hypersexuality, and binge eating), other impulsive-compulsive behaviors ([ICBs] punding, hobbyism, and walkabout) and dopamine dysregulation syndrome (compulsive PD medication overuse; Voon and Fox, 2007; Weintraub et al., 2015), even at early stages of the disease (mild parkinsonism) (Baig et al., 2017). With the exception of dopamine dysregulation syndrome, both ICDs and ICBs are considered behavioral addictions (Potenza, 2006) and their development in patients with PD is mainly related to the use of dopaminergic D_2/D_3 receptor (D_2R/D_3R) agonists (Weintraub et al., 2015), which can also provoke ICDs in

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patients with other diseases (Grall-Bronnec et al., 2018). Despite the serious consequences on the personal, familial, and social life of sufferers (Phu et al., 2014; Voon et al., 2011), little is known about the pathophysiology of these disorders. In fact, much of the information currently available has come from clinical and neuroimaging studies (Aracil-Bolaños and Strafella, 2016; Jiménez-Urbieta et al., 2015; Rizos et al., 2016; Weintraub et al., 2010), indicating that exaggerated dopaminergic stimulation in the ventral (limbic) striatum provokes functional changes to the elements of the associative/limbic circuits in the basal ganglia and cortex that are involved in reward processing (Voon et al., 2017). However, the dorsal striatum may also be involved, as functional and anatomical alterations to this structure were found in pathological gamblers (Boileau et al., 2014; van Holst et al., 2012) and in PD patients with ICDs (Premi et al., 2016).

To better understand the pathophysiological mechanisms underlying such behaviors, it is useful to carry out studies in animal models that reproduce such phenomena. Some studies have been carried out on different models of parkinsonism, after dopaminergic drug administration and using several behavioral tests (Cenci et al., 2015). Nevertheless, further studies are needed, in part because the behavioral tests used involve artificial scenarios or they do not strictly reflect any construct of impulsivity, or only limited aspects of them. As such, the place preference and self-administration paradigms most specifically evaluate the rewarding/addictive properties of dopaminergic drugs (Cenci et al., 2015), intracranial self-stimulation is an artificial positive reinforcer (Cenci et al., 2015; Holtz et al., 2016), the test of gambling-like behavior (rodent betting task) only assesses decision-making (Tremblay et al., 2017), the fixed consecutive number and low rate of responding schedules exclusively determine waiting impulsivity (Engeln et al., 2016), and the post-training signal attenuation task only establishes the effects on perseverative, "compulsive-like" behavior (Dardou et al., 2017). Because impulsive behaviors in PD are complex, studies with a paradigm that simultaneously measures several aspects of the ICBs are needed. In this context, the 5-choice serial reaction time task (5-CSRTT) is an interesting test as it evaluates attention control, waiting impulsivity, and compulsivity (Robbins, 2002). In particular, waiting impulsivity seems to be critical in substance addictions, which have similarities to the behavioral addictions observed in PD (Jiménez-Urbieta et al., 2015; Voon, 2014). Alternatively, there is considerable variation in the different drugs (L-dopa and different dopaminergic agonists such as ropinirole or pramipexole [PPX]) and administration paradigms (acute or 2–4 weeks treatments, different doses) used in the studies performed to date (Carvalho et al., 2017; Dardou et al., 2017; Engeln et al., 2016; Holtz et al., 2016; Rokosik and Napier, 2012; Tremblay et al., 2017). Nevertheless, the strong relationship detected between the duration of PPX treatment and ICDs in patients with PD (Grall-Bronnec et al., 2018) suggests that it might be worthwhile testing long-term treatment paradigms in which this dopaminergic agonist is administered.

In addition, it is known that there is an increase in FosB/ΔFosB expression in the striatum of rats treated with psychostimulant drugs (Nestler, 2001), as well as in rats with food addiction–like behavior (Velázquez-Sánchez et al., 2014). Hence, these transcription factors would appear to play a role in drug and behavioral addiction. In this sense, there was an increase in striatal FosB/ΔFosB in parkinsonian rats delivered with subchronic amounts of PPX or in those self-administering PPX (Engeln et al., 2013a; Loiodice et al., 2017). However, it remains unclear whether these changes are linked to impulsivity.

Our aim here was to use the 5-CSRTT paradigm to study the behavioral effects of chronic PPX administration in a rat model of mild, bilateral parkinsonism. This approach should allow us to analyze different aspects of ICBs in the context of parkinsonism and dopaminergic treatment. In addition, we investigated whether FosB/ΔFosB expression might also be associated with any abnormal behavior observed in this model. The data obtained suggests that this model may be useful to investigate the development of ICDs in patients with PD.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (n = 29, 250 g at beginning of behavioral training; Harlan laboratories, Barcelona, Spain) were housed in pairs on an inverted 12h light-dark cycle in controlled conditions: 70% humidity and at 22 °C. Testing and feeding were carried out during the dark phase. The experimental procedures were approved by the ethics committee for animal research at Biodonostia Health Research Institute (San Sebastián, Spain), and they were carried out in accordance with the Spanish Government (RD 53/2013) and European Union (Directive 2010/63/EU) guidelines.

2.2. Stereotactic surgery

Rats were anesthetized with oxygen isoflurane, placed in a stereotactic frame (Stoelting Co, Wood Dale, IL) and injected with 2/9 serotype adeno-associated viral vectors encoding either human A53T mutated α-synuclein (α-syn: Lesion group, 9.6×10^{12} viral vector genomes-vg/mL) or green fluorescent protein (control group, 6.7×10^{13} vg/mL) at 2 co-ordinates of the substantia nigra *pars compacta* (SNpc: 1 μL per site, rate 0.2 μL/min): (1) anteroposterior -4.9, lateral ±2.2, ventral -7.7 mm; and (2) anteroposterior -5.4, lateral ±2.0, ventral -7.7 mm from Bregma and dura (Engeln et al., 2013b). As an analgesic, rats received a subcutaneous injection of Buprenorphine (0.05 mg/kg) 20–30 minutes before surgery.

2.3. Drugs

Pramipexole dihydrochloride (A1237; Sigma-Aldrich, St. Louis, MO) was dissolved in 0.9% NaCl and it was administered subcutaneously (s.c.) once daily at 0.25 mg/kg over 4 weeks. The dose was chosen based on previous studies in which it improved parkinsonism (Rokosik and Napier, 2012) and had reinforcing properties (Engeln et al., 2013a).

2.4. Adjusting stepping test

The adjusting stepping test was used to monitor the lesion's effects in vivo (Olsson et al., 1995) (see Supplementary Materials and Methods). The average number of adjusting steps in both directions (adduction and abduction) with each forepaw was considered in the analysis.

2.5. Five-choice serial reaction time task

The 5-CSRTT was performed in standard operant conditioning chambers placed in sound-attenuated and ventilated boxes (Med Associates Inc, St. Albans, VT). The scheduling and data collection of experimental events were controlled automatically by the Med-PC software (Med Associates Inc, St. Albans, VT), and the timeline of the 5-CSRTT procedures is detailed in the Supplementary Materials and Methods.

After a period of pretraining, animals were trained to respond (nose-poke) to brief flashes of light presented randomly at 1 of 5

spatial locations (see Supplementary Materials and Methods for details). Responses in the aperture where the visual stimulus was presented were recorded as correct responses and were rewarded by a food pellet delivery in the magazine feeder. Response errors were recorded as omissions (failures to respond within 5 seconds (limited hold period)), incorrect responses (responses made at the wrong location—any other aperture but the one with the light), and premature responses (responses made before the presentation of the visual stimulus in any of the 5 apertures). These response errors were all punished with a 5-s period of darkness (time-out) during which no food was delivered. Perseverative responses (additional responses in an aperture after a correct response) produced no time-out punishment period. After the retrieval of a food pellet from the food magazine following a correct response or a time-out period following either an incorrect response or an omission, the next trial was initiated. A premature response restarted the same trial.

The measurements recorded were the number of correct responses, the number of incorrect responses, the total number of trials responded (correct responses + incorrect responses), accuracy (correct responses/[correct + incorrect responses] × 100), the percentage omissions (number of omissions/[correct + incorrect responses + omissions] × 100), the number of premature responses, the number of perseverative responses, latency to correct responses (time from light presentation to a correct nose-poke), and latency to collect the reward (time to food pellet retrieval after a correct response). Because the pharmacological state (OFF or ON) influences the number of responded trials, which in turn influences the number of premature and perseverative responses, we assessed the rate of these both types of responses The number of premature or perseverative responses in each test session is influenced by the number of responses and omissions, which are in turn influenced by the pharmacological state (OFF or ON). Hence, we used the rate of premature and perseverative responses to make sessions comparable, calculated as rate of premature responses = premature responses/(correct + incorrect responses); and rate of perseverative responses = perseverative responses/(correct + incorrect responses). This parameter was chosen based on other corrections used in the literature in other situations (Amitai and Markou, 2011; Dalley et al., 2007; Isherwood et al., 2017; Koskinen et al., 2003; Moreno et al., 2013; Pezze et al., 2007; Winstanley et al., 2003).

The premature responses are considered as an expression of waiting impulsivity, whereas perseverative responses reflect compulsivity/cognitive inflexibility, and accuracy is the main outcome of attention performance. Omissions are influenced by features such as attention and motivation. Processing speed (latency to a reward or correct response) can be interpreted in different ways depending on the context (Amitai and Markou, 2011; Asinof and Paine, 2014).

2.6. Experimental design

Before 5-CSRTT training, rats were gradually food-deprived (20–10 g/rat/day) until they reached approximately 90% of their free-feeding body weight, thereafter establishing their intake at 15 g/rat/day. Only animals who reached the performance criteria of the 5-CSRTT on 5 consecutive days (accuracy >80%, omissions <20%; 60 sessions within 12 weeks of training; presurgery condition; n = 26) were randomly assigned to either the control (n = 9) or lesion (n = 17) groups and underwent stereotactic surgery. Bradykinesia was assessed using the adjusting stepping test 1 week before surgery and every 2 weeks after surgery until week 17, based on previous studies that show an established dopaminergic lesion at this time point (Fig. S1: Bourdenx et al., 2015).

After surgery, rats were left for 3 days to recover before starting PPX treatment. Afterward, in the first 11 weeks after surgery, rats were trained twice weekly in the 5-CSRTT and they were then trained 6 days a week until week 17 (Fig. S1). At this point, all control (n = 9) and lesion (n = 17) rats were treated chronically with PPX for 4 weeks, administered in a single daily dose at 0.25 mg/kg/d. The behavioral evaluation in the ON state was undertaken 1 hour after drug administration and the OFF state evaluation was undertaken before drug administration.

The 5-CSRTT was evaluated under the following times conditions (Fig. S1): basal state (presurgery; mean of = 5 days); 17 weeks after surgery (pretreatment; mean of = 3 days); and in the ON and OFF state 1, 2, 3, and 4 weeks after treatment onset. The OFF (before PPX administration) and ON (1 hour after PPX administration) states were evaluated every other day during the treatment to avoid excessively long evaluations on the same day. The average of the measurements obtained each week for the ON and OFF states was analyzed, and the animals were sacrificed for histological studies 3 days after the last 5-CSRTT test session (Fig. S1).

2.7. Brain tissue

Rats were anesthetized with a mixture of oxygen isoflurane (5%) and perfused transcardially with 4% paraformaldehyde. The rat's brain was removed and postfixed in the same fixative for 24 hours, and then cryoprotected in 30% sucrose. Serial coronal sections (40-μm thick) were obtained on a freezing microtome (SM2010R; Leica Biosystems, Nussloch, Germany) and stored at −20 °C in a cryoprotectant solution.

2.8. Immunohistochemistry

Immunohistochemistry was performed on free-floating sections containing the striatum and SNpc, as described previously (Engeln et al., 2013a; Quiroga-Varela et al., 2017), and using the following primary antibodies (see Supplementary Material and Methods): goat anti-DAT (1:100; sc-1433; Santa Cruz Biotechnology, Inc, Dallas, TX), rabbit anti-FosB/ΔFosB (1:500; sc-48; Santa Cruz Biotechnology, Inc, Dallas, TX), and mouse anti-TH (1:1000; MAB-5280; EMD Millipore HQ, Billerica, MA).

2.9. Quantification of striatal dopamine transporter and FosB/ΔFosB immunoreactivity

Microphotographs of striatal immunostained sections were obtained on a Nikon Eclipse 801 microscope (dopamine transporter (DAT) n = 9 sections/animal, 1X objective; FosB/ΔFosB n = 6 sections/animal, 10× objective). The optical density of DAT immunoreactivity was obtained using ImageJ (National Institute for Health, NIH) in 4 subregions of the caudate putamen (CPu) as described previously (Quiroga-Varela et al., 2017): dorsolateral (DL); ventrolateral (VL); dorsomedial (DM); and ventromedial (VM). FosB/ΔFosB immunoreactive neurons in the CPu (DL, VL, DM, VM) and nucleus accumbens (NAc; core and shell) were quantified using an automatic triangle thresholding method in ImageJ. A region of constant size (0.56 mm^2) was used as a reference area (Gago et al., 2011).

2.10. Stereological counting of tyrosine hydroxylase immunoreactive neurons in the SNpc

The TH^+ neurons present in the SNpc were counted by unbiased design-based stereology on a Bx61 microscope (Olympus, Hicksville, NY, USA) equipped with a DP71 camera (Olympus NY, USA) and with a stage connected to an xyz stepper (H101BX, PRIOR)

driven by the CAST Visiopharm software (Hoersholm, Denmark). Stereological counting was performed using the optical fractionator method every fourth section throughout the entire rostrocaudal extent of the SNpc (for further details see Supplementary Materials and Methods).

2.11. Statistical analyses

All analyses were carried out using the SigmaStat software (version 3.5, SPSS, Inc, Chicago, IL). Normality was assessed using the Kolmogorov-Smirnov test and variance equality by Lavene's test. The stepping test (control vs. lesion groups) was analyzed using the Mann-Whitney *U* test. Variables derived from the 5-CSRTT were analyzed at different time points using Friedman repeated measures ANOVA followed by a *post hoc* Tukey's test for multiple comparisons. Differences between control and lesion groups at each time point were set by the Mann-Whitney *U* test. Changes in the expression of histological biomarkers between groups and between the CPu subregions within a group were analyzed using the Mann-Whitney *U* test. Correlation analysis was performed using the nonparametric Spearman test. The values of the statistical analysis and the corresponding *p* value are shown in Table S1. The statistical significance was set at $p < 0.05$.

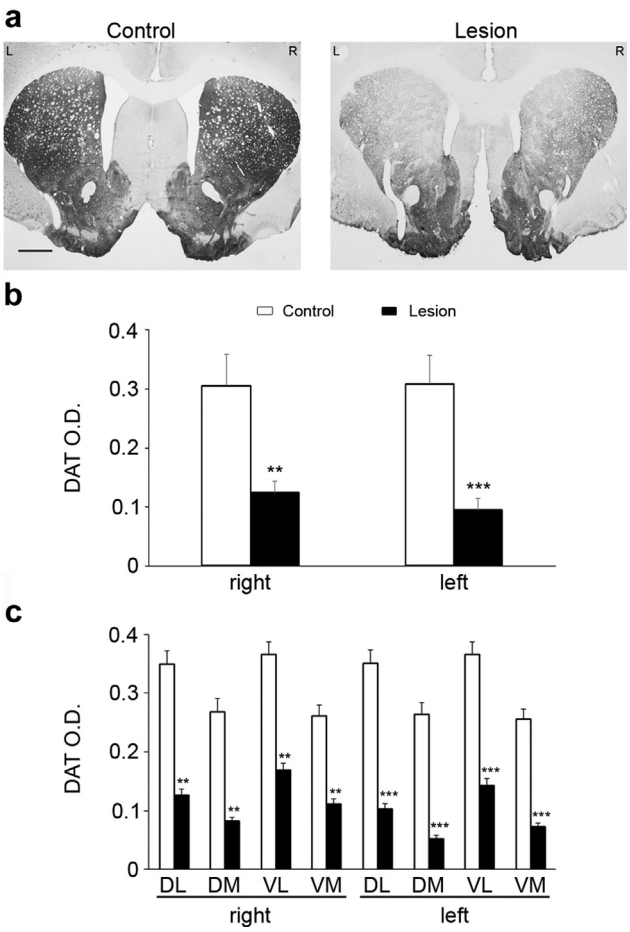

Fig. 1. Dopamine transporter (DAT) expression in the striatum. (A) Representative photomicrographs of coronal striatal sections from control and lesion animals immunolabeled for DAT (scale bar, 1 mm). (B and C) Relative optical density (O.D.) of DAT in the whole caudate putamen (CPu) (B) and in its 4 striatal subregions (C). The values are expressed as the mean ± SEM (n = 9 slices/animal: control n = 9, lesion n = 17). $^{**}p < 0.01$, $^{***}p < 0.001$ versus control. Abbreviations: L, left; R, right; DL, dorsolateral; DM, dorsomedial; VL, ventrolateral; VM, ventromedial.

3. Results

3.1. Motor impairment and dopaminergic lesion

The number of adjusting steps fell significantly and progressively in the lesioned animals relative to the control rats from the 7th (14% reduction, $p < 0.01$) until the 17th week after surgery (47% reduction, $p < 0.001$; Fig. S2, Table S1).

In the lesion group there was a 64% reduction in striatal (CPu) DAT compared with the control rats ($p < 0.01$; Table S1) and this reduction was significant in both hemispheres of the whole CPu (right $p < 0.01$; left $p < 0.001$), as well as in the distinct striatal subregions studied (right $p < 0.01$ each region; left $p < 0.001$ each region; Fig. 1A–C and Table S1). Moreover, DAT expression was significantly lower in the medial (DM+VM) than in the lateral (DL+VL) CPu of lesion animals ($p = 0.046$). Stereological analysis of TH^+ neurons in the SNpc of the lesion rats indicated a significant 43% reduction of dopaminergic cells relative to the control rats ($p < 0.001$), which was also significant in both hemispheres (right $p < 0.01$; left $p < 0.001$; Fig. 2, Table S1).

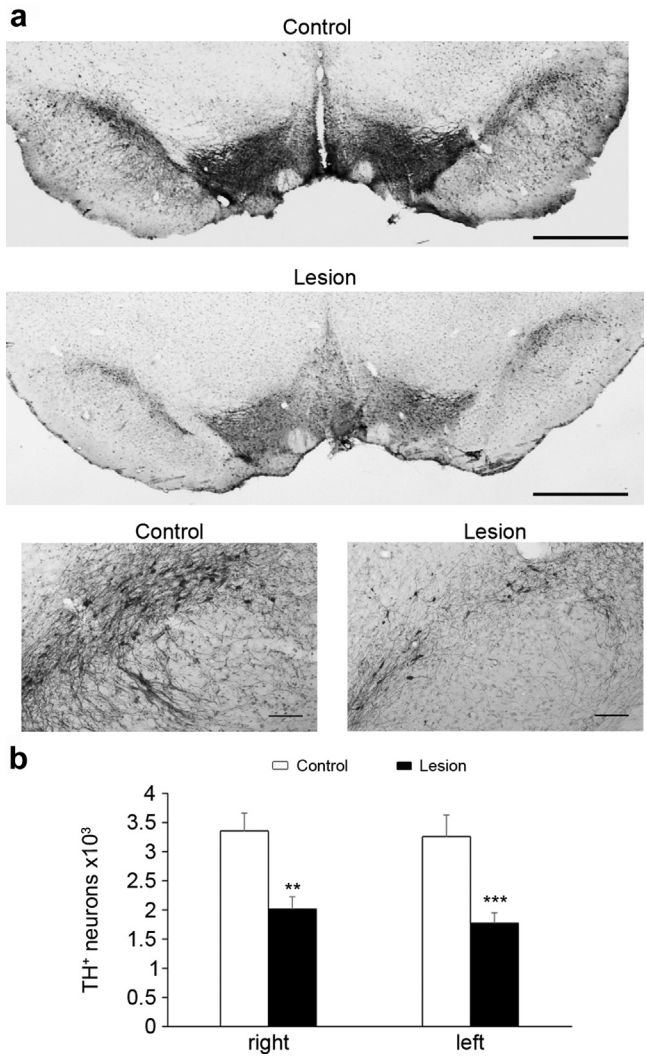

Fig. 2. Neurons expressing tyrosine hydroxylase (TH) in the substantia nigra *pars compacta* (SNpc). (A) Representative photomicrographs of coronal TH-immunostained nigral sections of control and lesion animals (scale bars, 1 mm and 100 μm). (B) Stereological quantification of the number of TH^+ neurons in control and lesion rats, expressed as the mean ± SEM (n = 7 slices/animal: control n = 9, lesion n = 17). $^{**}p > 0.01$, $^{***}p < 0.001$ versus control.

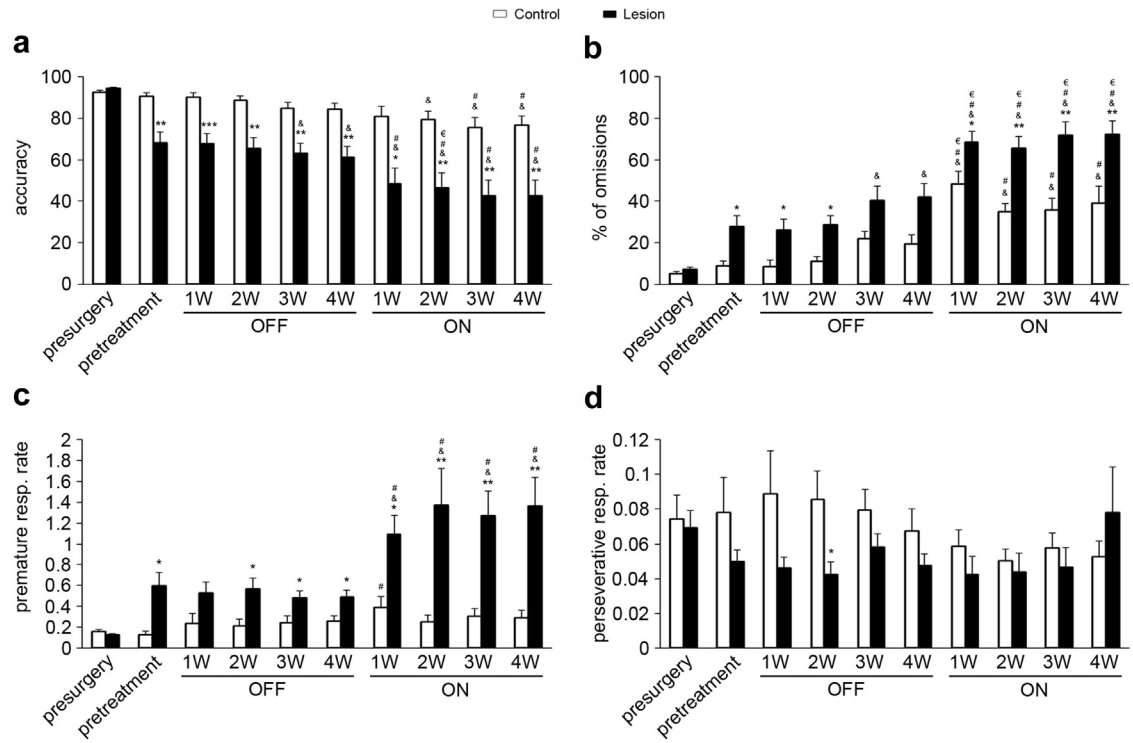

Fig. 3. Effect of mild bilateral dopaminergic depletion and chronic PPX treatment on the 5-choice serial reaction time task (5-CSRTT). Behavioral parameters of control and lesion animals were measured before surgery, before treatment, and weekly throughout the chronic PPX treatment (4 weeks), in the ON and OFF state: (A) accuracy, (B) percentage of omissions, (C) rate of premature responses (premature responses/[correct + incorrect responses]), (D) perseverative responses rate (perseverative responses/[correct + incorrect responses]). The data are expressed as the mean ± SEM (control n = 9, lesion n = 17); $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus control, $^{\&}p < 0.05$ versus presurgery, $^{\#}p < 0.05$ versus pretreatment, $^{€}p < 0.05$ versus OFF.

3.2. Changes in 5-CSRTT induced by dopaminergic lesion and PPX treatment

3.2.1. Effect of the dopaminergic lesion

No significant differences in any variable were evident between the 2 groups before surgery (Fig. 3 and Fig. S3, Table S1). By contrast, 17 weeks after surgery (pretreatment) there was a significant reduction in accuracy ($p < 0.01$), a higher percentage of omissions ($p < 0.05$), a higher rate of premature responses ($p < 0.05$), and longer latencies for correct responses ($p < 0.01$), and reward retrieval ($p < 0.05$) in lesion rats (Fig. 3 and Fig. S3, Table S1). Conversely, the rate of perseverative responses was no different between the 2 groups (Fig. 3D, Table S1).

3.3. Effect of chronic PPX administration

3.3.1. Lesion versus control groups

In both the ON and OFF states, there was a significant decrease in accuracy in lesioned animals relative to the control rats (Table S1) throughout the treatment period ($p < 0.05$, $p < 0.01$; Fig. 3A). In addition, in the ON state, in the lesioned rats, there was a significant increase in the percentage of omissions ($p < 0.05$, $p < 0.01$; Fig. 3B) and in the premature responses ($p < 0.05$, $p < 0.01$; Fig. 3C) during the 4 weeks of treatment, and in the latency for correct responses in the 2nd ($p < 0.05$) and 4th weeks ($p < 0.01$; Fig. S3). In the OFF state, a significant increase in the percentage of omissions was observed in the first 2 weeks ($p < 0.05$; Fig. 3B) and in the premature responses rate from the 2nd week ($p < 0.05$; Fig. 3C), as well as a significant reduction in the perseverative responses rate in week 2 ($p < 0.05$; Fig. 3D).

3.3.2. Effect throughout the treatment in each group

In the animals of the lesion group, there was a significant reduction in accuracy ($p < 0.05$) and more omissions ($p < 0.05$), as well as a higher rate of premature responses ($p < 0.05$; Fig. 3A–C) and a longer latency for correct responses ($p < 0.05$; Fig. S3 and Table S1) throughout the treatment relative to the presurgery and pretreatment times. The reward retrieval latency was only higher after 1 week of treatment ($p < 0.05$; Fig. S3) and no differences were evident in the rate of perseverative responses with respect to the presurgery and pretreatment conditions (Fig. 3D). In the OFF state, there was a significant reduction in accuracy ($p < 0.05$) and an increase in the omissions ($p < 0.05$; Fig. 3A and B) and in the latency for correct responses during the 3rd and 4th weeks of treatment ($p < 0.05$) relative to the performance presurgery (Fig. S3). Comparing both states, the accuracy in the ON state was worse at 2 weeks and the percentage of omissions was higher at 4 weeks (Fig. 3 and Fig. S3).

In the control group (Table S1), there was a significant reduction in accuracy in the ON state from the 2nd week of treatment ($p < 0.05$) relative to presurgery, and in the 3rd and 4th weeks relative to pretreatment ($p < 0.05$; Fig. 3A). There was also an increase in omissions ($p < 0.05$) and of the latency to a correct response during the entire treatment relative to both the presurgery and pretreatment values ($p < 0.05$; Fig. 3B and Fig. S2). An increase in the rate of premature responses after the first week of treatment was also evident relative to the pretreatment period ($p < 0.05$; Fig. 3C). The reward retrieval latency was longer after 1 and 2 weeks than pretreatment ($p < 0.05$; Fig. S3). By contrast, no significant difference was observed for any variable in control rats in the OFF state (Fig. 3 and Fig. S3). Comparing both states, the only difference was in the higher proportion of omissions at week 1 in the ON state (Fig. 3 and Fig. S3).

3.4. Striatal FosB/ΔFosB expression

The FosB/ΔFosB expression was stronger in the whole CPu (Lesion 1611 nuclei/mm^2, Control 1288 nuclei/mm^2; $p < 0.05$) and in the NAc (Lesion 1936 nuclei/mm^2, Control 1654 nuclei/mm^2; $p < 0.05$) of the Lesion rats than in the Control animals. In terms of the distinct subregions, the FosB/ΔFosB expression was significantly higher in the right DL ($p < 0.01$) and VL ($p < 0.05$), NAc core ($p < 0.05$) and NAc shell ($p < 0.05$; Fig. 4B, Table S1), as well as in the left DL ($p < 0.01$) and VL ($p < 0.05$; Fig. 4C, Table S1) of the lesion rats.

3.5. Correlations between the behavioral and histological parameters

Distinct correlation analyses were performed (Fig. 5). In parkinsonian rats (lesion group), a spearman correlation analysis showed that the rate of premature responses at the pretreatment time point was positively correlated with the rate of premature responses in both the ON and OFF states during the whole treatment (OFF state, $p < 0.001$ at each week; ON state, $p < 0.01$ weeks 1, 2, and 3, and $p < 0.05$ weeks 4; Table S1). In addition, there was a significant negative correlation between the striatal DAT optical density and the rate of premature responses at the pretreatment time point ($p < 0.01$), as well as that in the OFF state during the whole experiment ($p < 0.01$ at each week; Table S1). No significant correlation was evident between the number of TH$^+$ neurons in SNpc and the rate of premature responses at any time point (Table S1). In the ON state, this correlation was only significant in week 3 ($p < 0.05$), whereas there was a tendency toward significance in week 4 ($p = 0.06$; Table S1). The FosB/ΔFosB expression in the whole CPu or in each of its subregions was not correlated with the rate of premature responses in either the lesion group or when the 2 groups of animals were considered together at any time point (data not shown). However, the striatal FosB/ΔFosB expression was negatively correlated with the DAT values in the whole CPu ($p < 0.05$) and in each hemisphere (right $p < 0.05$; left $p < 0.05$) when the control and lesion groups were considered together (Table S1). In terms of the CPu subregions, this inverse correlation with DAT density was also observed in the DL ($p < 0.01$) and VL ($p < 0.01$) of the right hemisphere, and in the 4 subregions of the left hemisphere (VL $p < 0.01$; DL, DM, VM $p < 0.05$; Table S1). Perseverative responses were not correlated with any histological or behavioral parameter (data not shown).

4. Discussion

We have analyzed the impulsive behavior induced by a mild bilateral dopaminergic lesion simulating early PD (Rodriguez-Oroz et al., 2009) and after the chronic administration of PPX, this resembling the clinical situation of de novo patients with PD treated with D_2R/D_3R dopaminergic agonists (see Fig. 5A for a summary of the results). The mild bilateral striatal dopaminergic denervation (64%) induces an increase in waiting impulsivity (the rate of premature responses), in keeping with another recent study in this model (Engeln et al., 2016) and on animals with bilateral 6-OHDA lesions in the DL CPu (Tedford et al., 2015) that performed different behavioral tasks. This is also consistent with the fact that although impulsivity is a multifactorial construct modulated by several neurotransmitters (the serotonergic, noradrenergic, opioid, and GABAergic systems), dopamine plays a pivotal role in this phenomenon (Cumming and Borghammer, 2011; D'Amour-Horvat and Leyton, 2014). However, impulsive-like behavior does not develop in parkinsonian models induced by bilateral injection of 6-OHDA into the SN and ventral tegmental area (Carvalho et al., 2017) or into the lateral CPu (DL+VL; Baunez and Robbins, 1999).

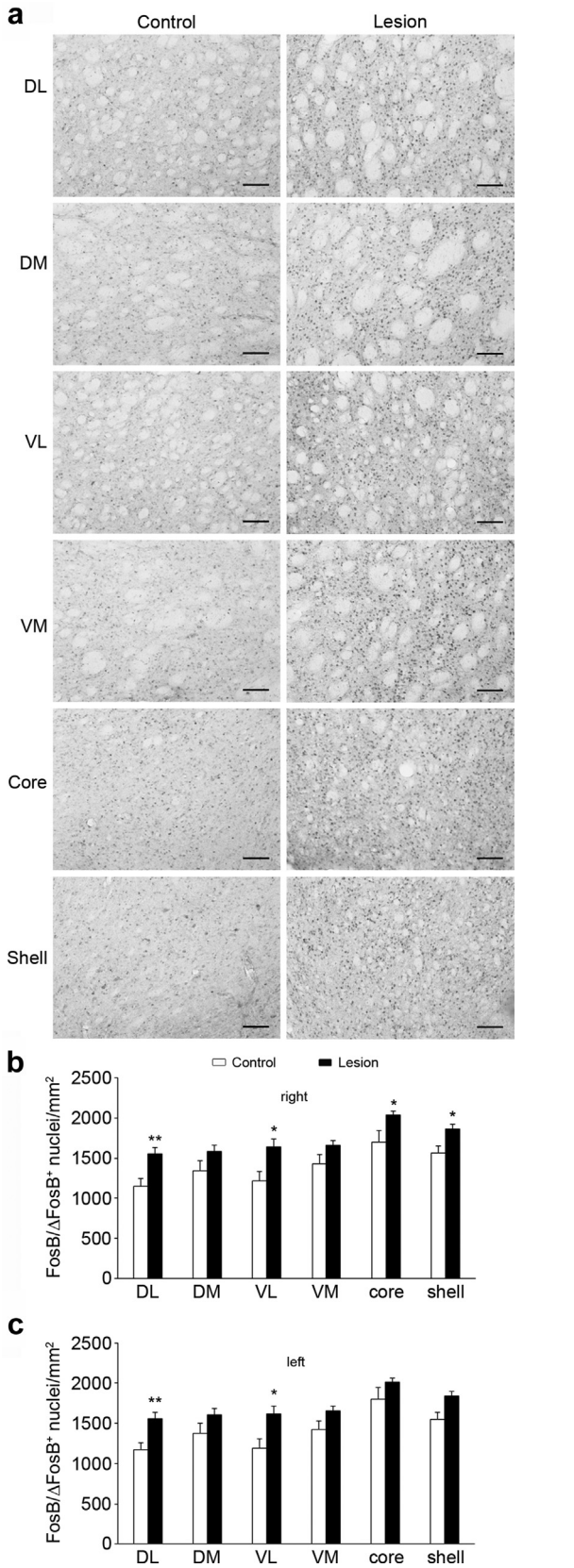

Fig. 4. The FosB/ΔFosB expression in the striatum. (A) Representative photomicrographs of FosB/ΔFosB-immunoreactive nuclear expression in the different striatal subregions of control and lesion animals (scale bars, 100 μm). (B) Quantification of the density of FosB/ΔFosB-immunoreactive nuclear profiles (number of nuclei profiles/mm^2) in the different subregions of the caudate putamen (CPu) and nucleus accumbens (NAc; core and shell) in control and lesion rats (n = 6 slices/animal: control n = 9, lesion n = 17). *$p < 0.05$, **$p < 0.01$ versus control. Abbreviations: DL, dorsolateral; DM, dorsomedial; VL, ventrolateral; VM, ventromedial.

a

WITHIN GROUPS VS PRESURGERY CONDITION

		accuracy	% of omissions	premature resp. rate	perseverative resp. rate	correct resp. latency	reward latency
LESION	ON	↓1-4W	↑1-4W	↑1-4W	↔	↑1-4W	↑1W
	OFF	↓3-4W	↑3-4W	↔	↔	↑3-4W	↔
CONTROL	ON	↓2-4W	↑1-4W	↔	↔	↑1-4W	↔
	OFF	↔	↔	↔	↔	↔	↔

WITHIN GROUPS VS PRETREATMENT CONDITION

		accuracy	% of omissions	premature resp. rate	perseverative resp. rate	correct resp. latency	reward latency
LESION	ON	↓1-4W	↑1-4W	↑1-4W	↔	↑1-4W	↑1W
	OFF	↔	↔	↔	↔	↔	↔
CONTROL	ON	↓3-4W	↑1-4W	↑1W	↔	↑1-4W	↑1-2W
	OFF	↔	↔	↔	↔	↔	↔

LESION VS CONTROL

condition	accuracy	% of omissions	premature resp. rate	perseverative resp. rate	correct resp. latency	reward latency
pretreatment	↓	↑	↑	↔	↑	↑
ON	↓1-4W	↑1-4W	↑1-4W	↔	↑2,4W	↔
OFF	↓1-4W	↑1-2W	↑2-4W	↓2W	↑1-4W	↔

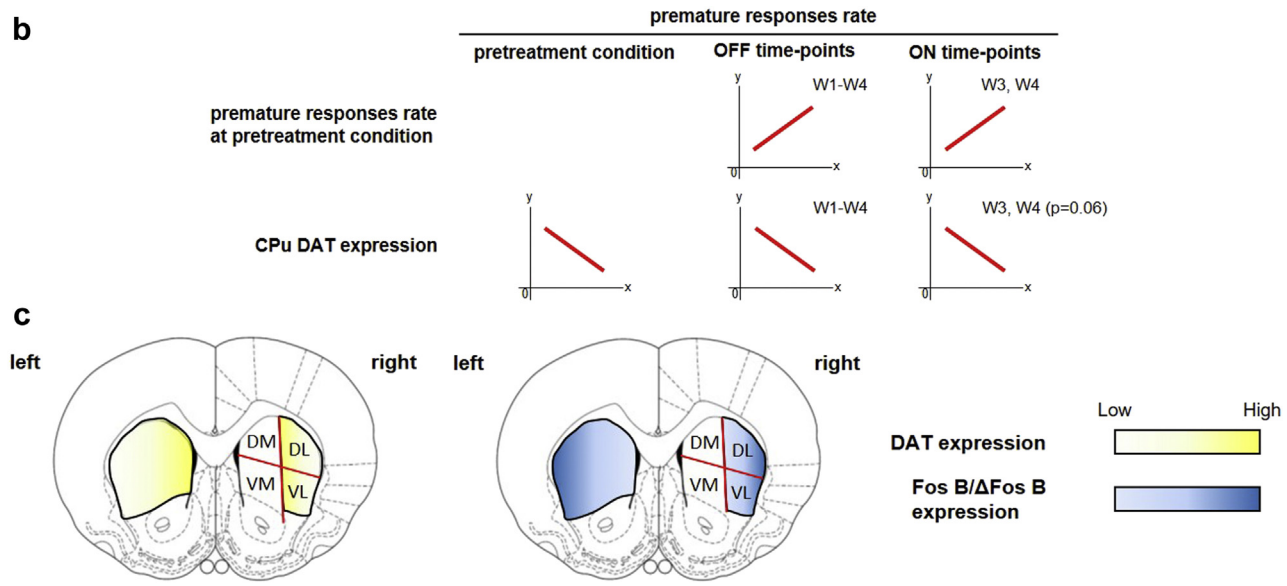

Fig. 5. Summary of the changes in the behavioral parameters measured in the 5-CSRTT (A) and the results of the correlation analysis (B–C). (A) Increase (↑) or decrease (↓) in the behavioral parameters recorded in each group relative to the presurgery (top row) and pretreatment values (middle row), and between groups (bottom row). (B) In parkinsonian rats, the rate of premature responses in the pretreatment state positively correlates with the rate of premature responses in both the ON (weeks 3 and 4) and OFF (weeks 1–4) states. The DAT expression in the CPu negatively correlated with the rate of premature responses at pretreatment and in the ON (week 3, week 4) and OFF state (1–4 weeks). (C) Considering the control and lesion groups together, the FosB/ΔFosB expression correlated negatively with the DAT expression in the entire CPu and in the 4 subregions (DL, dorsolateral; DM, dorsomedial; VL, ventrolateral; VM, ventromedial) of the left hemisphere, and the whole CPu and in the DL and VL subregions of the right hemisphere. Abbreviations: 5-CSRTT, 5-choice serial reaction time task; CPu, caudate putamen.

Differences may reflect the severity and topography of the dopaminergic lesion produced, as well as the distinct tests used to evaluate impulsivity (variable delay-to-signal, probability discounting task—rodent betting task). These data suggest that the pattern and severity of dopaminergic denervation are relevant to the impulsive behavior in parkinsonian rats. In this sense, it is important to note that the dopaminergic neurons in the ventral tegmental area are preserved in the model used in this study (Engeln et al., 2013b; Maingay et al., 2006). This preservation is in keeping with recent studies showing that not only the ventral (Cilia et al., 2010; Vriend et al., 2014), but also the dorsal striatum may play a role in pathological gambling (Boileau et al., 2014; van Holst et al., 2012), as well as in ICDs in patients with PD (Premi et al., 2016).

Waiting impulsive behavior was exacerbated under the effect of chronic PPX from the first week of treatment, indicating that dopaminergic agonists are indeed the main risk factor for ICD development in patients with PD (Weintraub and Claassen, 2017). Interestingly, we also found that from the second week of treatment onward, it is important to note that the enhanced waiting impulsivity of parkinsonian rats in the OFF medication state persisted throughout the treatment was similar to that of pretreatment, which may reflect the premature response induced by dopamine depletion. This finding resembles the fact that ICD in patients with PD is not only evident under the acute effect of medication but rather as a continuum. Moreover, impulsivity in both the ON and OFF states is better correlated with the impulsivity induced by the dopaminergic lesion alone and not with basal impulsivity. As such, dopaminergic denervation can apparently affect impulsivity profoundly and subsequent chronic treatment with dopaminergic agonists may enhance the impulsive behavior in the most vulnerable parkinsonian rats.

A higher degree of striatal denervation appears to be linked with the development of impulsive behavior because of lesion and PPX

administration in the final weeks of treatment. Thus, patients with PD with stronger nigrostriatal denervation at the moment of diagnosis might produce a subclinical impulsive trait and it would be more prone to develop into abnormal ICD when treated with a D_2R/D_3R dopaminergic agonist. Indeed, although the prevalence of ICDs is similar in untreated patients with PD and healthy controls (Antonini et al., 2011; Cilia et al., 2011; Weintraub et al., 2013), untreated patients with PD display a stronger intertemporal choice (a preference for sooner but smaller rewards rather than later but larger ones), indicating that dopaminergic denervation itself can alter behavioral processes relevant to ICD (Al-Khaled et al., 2015; Milenkova et al., 2011). In addition, striatal dopaminergic denervation at diagnosis is stronger in patients that develop ICD after dopaminergic treatment than in those that remain free of ICD symptoms (Vriend et al., 2014).

The increase in omissions and the longer latencies, as well as the decrease in accuracy after bilateral dopaminergic lesion that is exacerbated by PPX, could be caused by a deficit in attention and/or motivation, or lesion-induced bradykinesia. However, this latter possibility could be dismissed as the PPX dose chosen was efficient in improving motor deficits (Rokosik and Napier, 2012). This is consistent with studies in which this behavior was related to the severity and topography of the striatal denervation in rats with bilateral CPu dopaminergic depletion (Baunez and Robbins, 1999; Favier et al., 2014). Indeed, attention and impulsivity are interrelated, particularly given that sustained attention is needed to suppress drug-seeking behaviors in addiction (de Wit, 2009) and impulsive individuals that score low in sustained attention tasks (Bakan task; Smith et al., 1991). Moreover, PPX reduces short-term verbal memory, verbal fluency, and attentional-executive functions (Brusa et al., 2003). In our experiments, the administration of PPX may reduce attention in lesioned animals, a reflection of the interaction between dopaminergic depletion and the dopaminergic drug, which could impair the accuracy, increase the omissions, and induce longer latencies. Attention and motivation account for omissions, as well as incorrect responses, such that we corrected the raw premature and perseverative responses using rates that take this fact into account. Further studies should be undertaken to explore the influence of PPX on attention and motivation during the performance of these tasks.

Interestingly, we did not observe any relationship between perseverative responses and PPX treatment in parkinsonian rats. Although there is a component of perseveration in gambling and punding, and they are currently considered as impulsivity-compulsivity spectrum disorders (Diagnostic and Statistical Manual of Mental Disorders, 5th ed. DSM–5, American Psychiatric Association, 2013), they share the impulsivity trait with the rest of abnormal impulsive behaviors (ICDs) in patients with PD treated with dopaminergic agonists. Hence, the lack of a correlation between PPX and perseveration could be due to the fact that the impulsive trait of punding and gambling is induced by PPX, as opposed to the perseverative/compulsive trait. Moreover, the results of a recent meta-analysis suggest that the compulsive tendencies of pathological gamblers are not directly related to the gambling behavior itself but rather, to both the development and the maintenance of gambling symptoms (van Timmeren et al., 2018).

Given their relevance to addiction (Cooper et al., 2017; Nestler, 2001), we analyzed FosB/ΔFosB expression and interestingly, these transcription factors were more strongly expressed in the lateral CPu (both right and left) and in the right NAc (both core and shell) of Parkinsonian animals, indicating a higher stronger involvement of the right hemisphere. This is in keeping with several studies showing that regions of the right hemisphere participate in impulsivity in PD. Indeed, right subthalamotomy is associated with greater risk of impulsivity and disinhibition (Obeso et al., 2017), and higher dopaminergic denervation in the right dorsal and ventral striatum has been described in patients with PD with an ICD (Voon et al., 2014; Vriend et al., 2014). However, we obtained no significant correlation between FosB/ΔFosB expressions in any striatal subregion with waiting impulsivity, although the levels of these transcription factors in the CPu were negatively correlated with the severity of striatal dopaminergic denervation in the right lateral CPu (motor CPu) and in the left 4 CPu subregions. Elsewhere, the enhanced FosB/ΔFosB expression in the medial regions of the CPu of parkinsonian rats was correlated with the rewarding effects of PPX (Engeln et al., 2013a). This discrepancy in the CPu region that correlates with the effects of PPX could be due to the model used, as bilateral depletion in both the CPu and NAc was obtained by a single intracerebroventricular injection of 6-OHDA and the animals were allowed to self-administer PPX intravenously, in contrast to the progressive SNpc degeneration we provoked. Importantly, L-DOPA administration causes an increment in FosB/ΔFosB expression in the CPu (Cenci et al., 1999), which is positively correlated with the severity of dyskinesia, a motor side-effect of dopamine replacement therapy (Andersson et al., 1999). Thus, further studies will be necessary to determine if the striatal expression of FosB/ΔFosB is associated to the expression of nonmotor behavioral complications or if it is simply because of dopaminergic treatment, and whether this is associated with a specific pattern of dopaminergic depletion.

In summary, we have demonstrated that a mild bilateral dopaminergic lesion, similar to that in patients with early PD, is linked to a more severe impulsive trait prompted by PPX administration, which seems to be related to the severity of dopaminergic depletion. All in all, we believe that the impulsivity trait associated with the dopaminergic lesion and its interplay with therapeutic D_2R/D_3R dopaminergic agonist administration makes the present model a useful tool to study how dopaminergic agonists affect the induction of pathological impulsivity in PD.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.11.021.

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