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Short communication

Electrolytic lesion of globus pallidus ameliorates the behavioral and neurodegenerative effects of quinolinic acid lesion of the striatum: a potential novel treatment in a rat model of Huntington's disease

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Abstract

Bilateral electrolytic pallidal lesion ameliorated the deleterious effects of bilateral quinolinic acid (QA) lesion to the striatum on post-surgery weight, activity level, and performance in a water maze task, and reduced the extent of striatal damage. Given that the neurodegenerative and behavioral effects of QA striatal lesion are thought to mimic those seen in Huntington's disease, these results may point to a potential novel treatment for this disease. © 1998 Elsevier Science B.V.

Keywords: Basal ganglia; Striatum; Globus Pallidus; Quinolinic acid; Lesion; Water maze; Huntington's disease; Rat

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder of mid-life onset, clinically characterized by progressive involuntary choreiform movements, cognitive decline, and personality changes [1–3]. The first and most severely affected neurons are in the striatum, particularly those projecting to the external segment of the globus pallidus (GPe) and the substantia nigra [4,1,5–8,2,3,9–13]. The leading model of HD, launched by Penney and Young [1,3], views this disease as resulting from abnormal functioning of basal ganglia–thalamocortical circuitry. More specifically, loss of striatal innervation to GPe leads to overactivity of GPe which results in underactivity of the subthalamic nucleus, which in turn leads to underactivity of the internal segment of the globus pallidus and thus overactivity of the thalamus [1,14,15,3].

On the basis of the pathological mechanism suggested to underlie the symptomatology of HD, we suggested that lesion of the overactive GPe should ameliorate some of the symptoms of HD [16]. In addition, since progressive striatal degeneration characteristic of HD may depend on corticostriatal excitatory input [17–19], basal ganglia–thalamocortical circuitry dysfunction postulated in HD could contribute to such degeneration via its effects on the frontal cortex. Therefore, we hypothesized that GPe lesion may not only ameliorate some of the symptoms of HD but also slow down the progressive striatal degeneration in this disease.

The present study tested these suggestions in the leading rat model of HD, namely, striatal quinolinic acid (QA) lesion, which has been shown to most closely mimic the selective neural degeneration in the striatum of HD patients [20,21,18,22]. Of particular importance for the suitability of the QA lesion model is that it apparently mimics two main characteristics of the pathological process underlying HD, namely, the progressive course of striatal neurodegeneration [HD: [2,11,12], QA: [23]] and the relative sparing of striatal neurons projecting to the internal segment of the globus pallidus (the entopeduncular nucleus in the rat) compared with striatal neurons projecting to the substantia nigra and GPe (globus pallidus (GP) in the rat) [HD: [4,5,9,10], but see Ref. [19]; QA: [24]]. In addition, QA striatal lesions have been shown to produce in rats motor and cognitive effects reminiscent of HD symptoms [e.g., Refs. [25,26]].

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The present study tested whether behavioral and neurodegenerative effects of QA lesions to the striatum can be ameliorated by lesions to the GP. The behavioral measures used were spontaneous activity and performance in a water maze task, both of which are known to be sensitive to striatal damage and have been previously suggested to resemble the behavioral pathology observed in HD [18,25,26]. In addition, the rats' post-surgery weight was assessed since transient weight loss is typically observed following striatal QA lesions [27,18,26]

Sixty male Wistar rats approximately 4 months old, weighing 310–400 g before surgery, were housed in pairs under reversed cycle lighting (lights on 1900–0700) with food and water freely available. For surgery, rats received 3 mg/kg diazepam, and 20 min later were anaesthetized with i.p. injection of Equithesin (3.0 ml/kg). Lesion coordinates were according to the atlas of Paxinos and Watson [28]. *Striatal lesion*: Thirty one gauge cannulas were vertically lowered into the brain through holes drilled in the skull. The coordinates were: 1.0 mm anterior to bregma, 2.5 mm lateral to the midline, and 4.3 mm ventral to dura. We infused 1 μl of QA at a constant rate over 3 min. The cannulas were left in place for additional 5 min, to reduce upward diffusion of the solution. QA (Sigma Chemicals) was dissolved in 1 N NaOH and diluted with phosphate buffer at pH 7.2 to a final pH of 7.4 and a concentration of 120 nmol/μl. *Pallidal lesion*: Bilateral electrolytic lesions were made by passing a constant (anodic) 0.5 mA, 5 s DC current via 0.3 mm electrodes, insulated except for the tip, which were vertically lowered into the brain through holes drilled in the skull. The coordinates were: 0.5 mm posterior to bregma, 2.6 mm lateral to the midline, and 5 mm and 6 mm ventral to dura. *Combined striatal and pallidal lesion*: Rats sustained bilateral QA lesion to the striatum and bilateral electrolytic lesion to the pallidum as above. *Sham lesion*: Rats underwent the same surgical procedure as striatal rats but 1 μl of vehicle was used instead of QA. An additional dose of 3 mg/kg diazepam was given about 30 min following surgery. Post-surgical maintenance followed closely the procedure described by Cromwell and Berridge [29]. In spite of intensive maintenance, eight of the 22 striatal rats died within the first 2 post-surgery days. Only one of the 16 rats with a combined lesion died, and none from the sham ($n = 10$) and pallidal ($n = 12$) groups. One striatal rat fell ill about 12 days post surgery and was excluded from behavioral testing. Thus, the number of rats tested was: 10 sham, 13 striatal, 12 pallidal, and 15 combined.

Rats were weighed on days 2, 4, 6, and 10 post-surgery, and weight for each rat was calculated as a percent of its pre-surgery weight. There was no weight loss in the sham

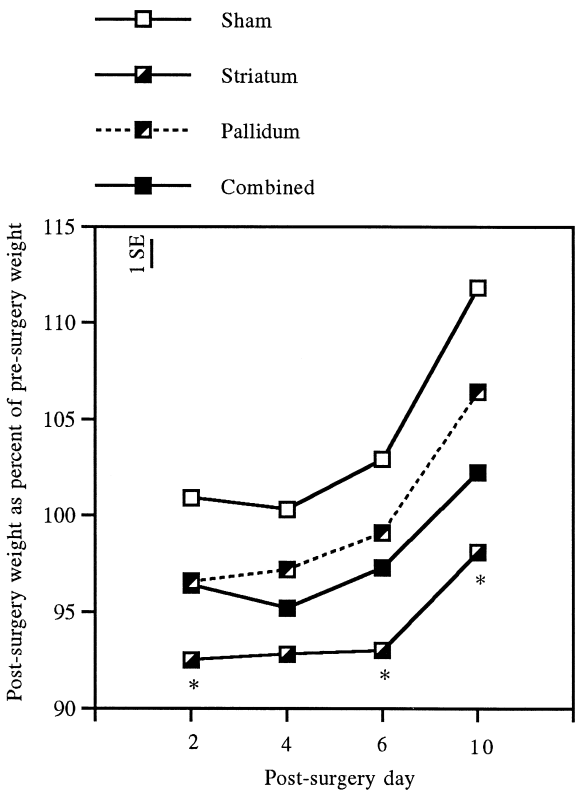

Fig. 1. The mean post-surgery weights, calculated as percent of pre-surgery weight of the sham, striatal, pallidal, and combined (striatal and pallidal) groups, on days 2, 4, 6, and 10 post-surgery. Asterisks indicate significant difference between the striatal and combined groups ($p < 0.05$, Student's *t*-test).

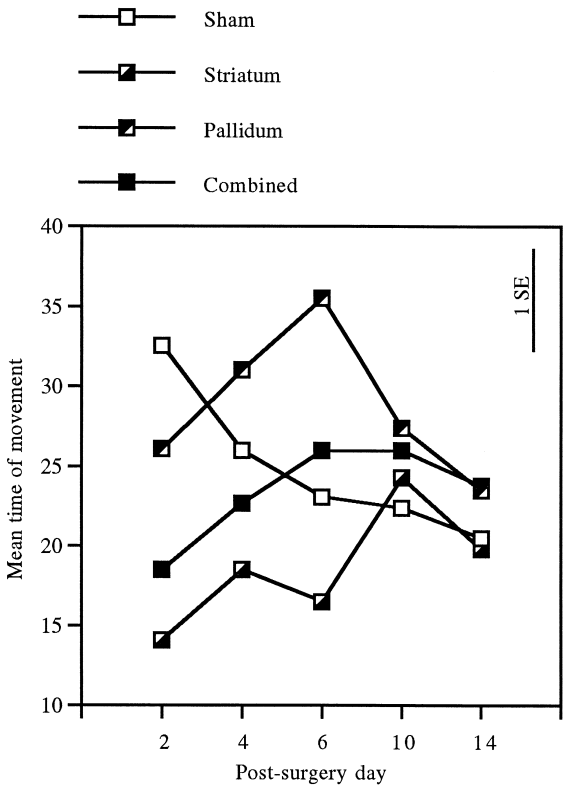

Fig. 2. The mean time of movement, in 6 min blocks, of the sham, striatal, pallidal, and combined (striatal and pallidal) groups, during 30 min free exploration sessions given on days 2, 4, 6, 10 and 14 post-surgery.

group; both the striatal and combined groups lost weight, but the loss was significantly smaller in the combined group (see Fig. 1; since the pre-surgery weights of eight pallidal rats were lost, only post-surgery weights of the remaining four pallidal rats are presented, although they are not included in the analysis). One-way ANOVA with a main factor of lesion and a repeated measurements factor of weighing yielded significant effects of lesion ($F(2,36) = 11.49$, $p < 0.0001$) and weighing ($F(3,108) = 29.97$, $p < 0.0001$) as well as the linear and quadratic trends of this factor (both $p < 0.0001$).

On days 2, 4, 6, 10 and 14 post-surgery, rats' activity was measured (Coulbourn Instruments' infrared motion activity monitor) during 30 min daily session of free exploration in plastic chambers ($46 \times 57 \times 37$ cm). Compared to sham rats which gradually reduced their activity throughout sessions, pallidal rats showed higher activity. Both striatal and combined rats showed lower activity, but this reduction was more pronounced in the striatal group (Fig. 2). One-way ANOVA with a main factor of lesion and repeated measurements factors of session and 6 min block yielded a significant lesion effect ($F(3,46) = 3.91$, $p < 0.05$), a significant quadratic trend of session ($F(1,46) = 9.71$, $p < 0.01$), and significant session × lesion interaction ($F(12,184) = 3.61$, $p < 0.0001$) as well as its linear and quadratic trends ($F(3,46) = 5.92$, $p < 0.01$ and $F(3,46) = 5.87$, $p < 0.01$, respectively).

Approximately 1 week following the last activity session, rats were tested in the water maze task in a circular pool (diameter = 137 cm, height = 35 cm) in which a transparent plastic platform (15.5×15.5 cm) was located below the water, invisible to the rat. On days 1–3 (acquisition), rats were given eight trials with the platform located in the center of the southwest quadrant, starting each trial at one of four starting locations (north, south, east, or west) in a pseudo-random order. If a rat found the platform, it was permitted to remain on it for 5 s. If it failed to find the platform for 60 s, it was taken out of the water and put on the platform for 5 s. Between trials, rats were kept in a holding cage for approximately 2 min. On day 4 (probe), rats were given four trials as in acquisition, and a 60 s probe trial, in which the platform was removed from the pool, was interposed between the 2nd and 3rd trials. On day 5 (reposition), rats were given four trials with the platform in the southwest quadrant, four trials in which the platform was repositioned in the center of the northeast quadrant, and additional two trials with the platform in its original location (southwest quadrant). On day 6 (visible platform), six trials were given during which the platform was visible (its top was covered with a black wooden

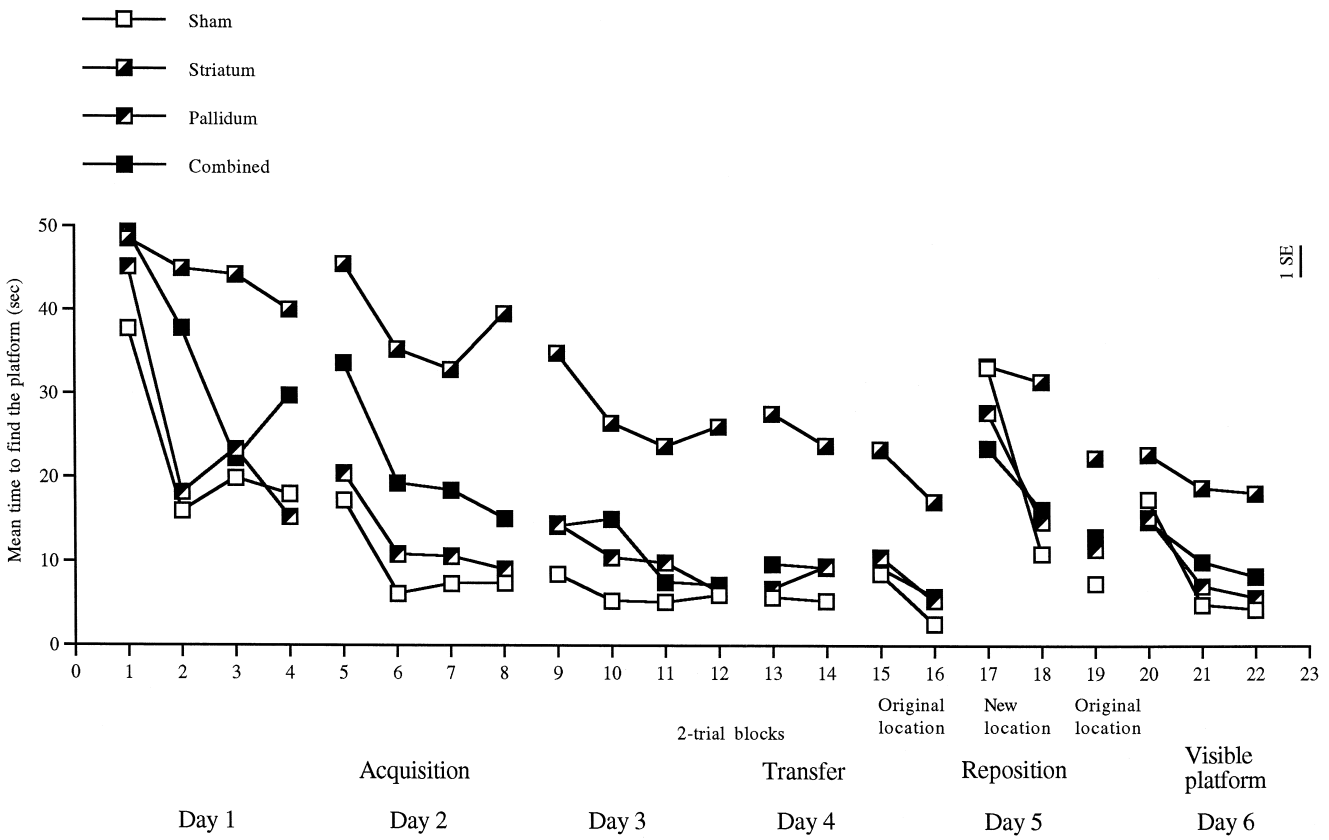

Fig. 3. Mean time, in two-trial blocks, of the sham, striatal, pallidal, and combined (striatal and pallidal) groups to find the platform in the different stages of the water maze task.

square plate which projected 2 cm above the surface of the water) and located in the southeast quadrant of the pool. The latency to find the platform on each trial was recorded. In addition, rats were monitored by a Sony camera for analysis of the probe trial.

Fig. 3 presents the mean time to find the platform, in two-trial blocks, of the sham, striatal, pallidal, and combined (striatal and pallidal) groups. As can be seen, rats with QA lesion to the striatum needed more time to find the hidden platform in the *acquisition* stage than the sham and the pallidal rats, which had highly similar times. In marked contrast, rats which sustained a combined striatal and pallidal lesion showed much better performance than striatal rats from day 1, and by day 3 reached shams' level of performance. One-way ANOVA with a main factor of lesion and repeated measurement factors of day and blocks yielded significant effects of lesion, day, and blocks ($F(3,46) = 14.76$, $p < 0.0001$, $F(2,92) = 84.54$, $p < 0.0001$, and $F(3,138) = 42.42$, $p < 0.0001$, respectively), as well as significant interactions of blocks × lesion, blocks × day, and blocks × day × lesion ($F(9,138) = 2.01$, $p < 0.05$, $F(6,276) = 4.28$, $p < 0.001$, and $F(18,276) = 1.71$, $p < 0.05$, respectively). *Reposition* of the platform led to increased latency to find the platform in all rats, which shortened with further training in the sham, pallidal and combined, but not in the striatal group. One-way ANOVA comparing the latency to find the platform in the last block prior to reposition with the first block after reposition yielded only a significant effect of reposition ($F(1,46) = 95.46$, $p < 0.0001$), whereas one-way ANOVA comparing the latency to find the platform in the two blocks after reposition yielded significant effects of lesion ($F(3,46) = 3.1$, $p < 0.05$) and block ($F(1,46) = 23.59$, $p < 0.0001$), as a well as a significant blocks × lesion interaction ($F(3,46) = 3.35$, $p < 0.05$). Finally, striatal rats were also slower to find the *visible platform* compared to the other groups which performed similarly. One-way ANOVA yielded significant effects of lesion ($F(3,46) = 3.50$, $p < 0.05$) and blocks ($F(2,92) = 27.33$, $p < 0.0001$), as well as significant linear and quadratic trends of blocks ($F(1,46) = 52.91$, $p < 0.0001$ and $F(1,46) = 7.07$, $p < 0.05$, respectively).

There were no differences between the four groups in the mean percent of time spent in each of the four pool quadrants during the 60 s probe trial in which the platform was removed from the pool, and all rats spent significantly

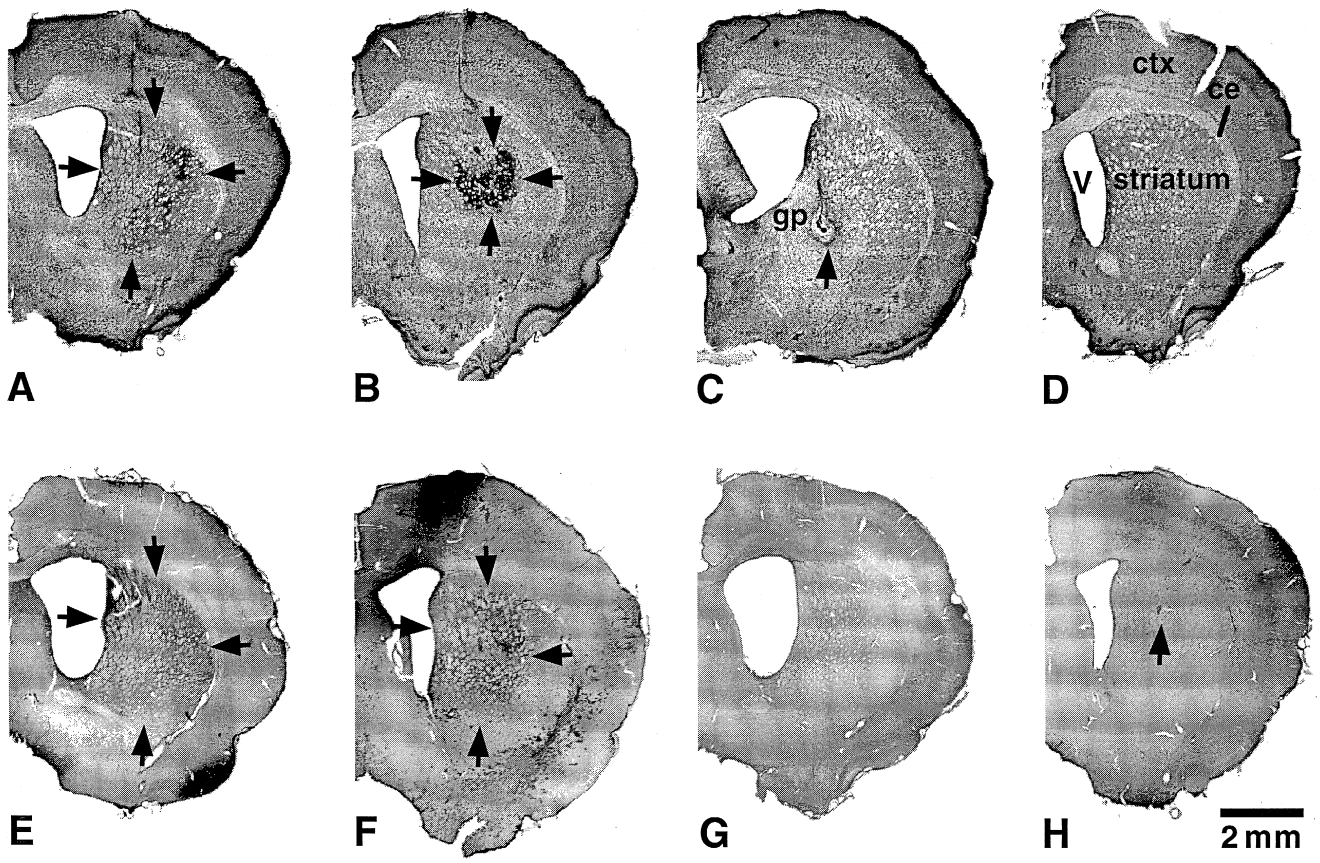

Fig. 4. Representative cresyl violet stained (A–D) and GFAP immunolabeled (E–H) coronal sections through the striatum. (A,E) The striatum of a rat sustaining striatal lesion only (the borders of the lesioned area are marked with arrows); (B,F) The striatum of a rat sustaining a combined striatal and pallidal lesion (the borders of the lesioned area are marked with arrows); (C) The pallidal lesion of this rat (marked with an arrow); (D,G) The striatum of a rat sustaining a pallidal lesion only; (H) The striatum of a sham operated rat.

more time in the quadrant where the platform was located during acquisition. One-way ANOVA with a main factor of lesion and a repeated measurements factor of quadrant yielded only significant effect of quadrant ($F(3,132) = 72.30$, $p < 0.0001$).

After the completion of the water maze task, 15 rats (3 sham, 4 striatal, 4 pallidal, and 4 combined) were randomly chosen for histological assessment. (The remaining rats are continuing behavioral testing). Rats were anaesthetized with an overdose of nembutal and perfused intracardially with 100 ml 0.1 M phosphate buffered saline (PBS) pH 7.4, followed by 150 ml 4% paraformaldehyde solution in PBS. Brains were postfixed for 2 h in the same fixative and then stored at 4°C in 30% sucrose in PBS. We cut 40 μm frozen coronal sections using a sliding microtome. Every fifth section was mounted and stained with cresyl violet and every other fifth section was processed for immunohistochemical labeling of glial fibrillary acidic protein (GFAP). The extent of the striatal lesions was determined according to the presence of neuronal cell degeneration, gliosis, and the presence of GFAP-labeled astrocytes. To quantify the size of the striatal lesion, images of coronal brain sections that contained the core of the lesions were captured for computer assisted image analysis. Striatal lesion size and the size of dorsal striatum on the right and left hemispheres were measured for each rat. The averages over the left and right hemispheres of these measures were compared between the striatal and combined (striatal and pallidal) groups. No difference in dorsal striatal size was found, suggesting no differential shrinkage or swelling of the brain as a result of lesion or fixation. The striatal lesions were located in the medial half of the striatum. The pallidal lesions were centered in GP or located along its medial and/or caudal borders. There were no signs of damage in the striatum of the rats sustaining sham or pallidal lesion only. Comparison of the average striatal lesion size in rats sustaining striatal lesion only with that of rats sustaining a combined striatal and pallidal lesion revealed that the extent of striatal damage in rats sustaining the combined lesion was more restricted than in rats sustaining striatal lesion only ($p < 0.05$, Mann–Whitney U rank test, Fig. 4).

Weight reduction and disruption of water maze performance following striatal lesion observed in the present study are similar to results reported in the literature [e.g., Refs. [27,30,18,25,26,31]]. Our finding of decreased activity level following striatal lesion contrasts with previous studies as these found an increase [26] or no change [32] in activity level. This inconsistency could stem from differences in time of testing post-surgery, the system used to monitor activity, or lesion site.

The major and novel finding of the present study is that bilateral electrolytic pallidal lesion reversed the behavioral effects of bilateral QA striatal lesion. It should be pointed out that while in the activity test this antagonism can be interpreted as reflecting additive effects of pallidal and striatal lesion, since the former led to increased and the latter to decreased activity compared with sham rats, no such interpretation can be applied to the water maze results, in which pallidal rats performed similarly to sham rats at all stages.

In addition, the extent of striatal damage in rats sustaining the combined striatal and pallidal lesion was more restricted compared to that seen in rats sustaining the same striatal lesion alone. Although the present results do not identify the source of the protective effect of the pallidal lesion, it is possible that the pallidal lesion slowed down the progressive neurodegeneration reported to occur after QA striatal lesion [23].

The mechanisms underlying the ameliorating behavioral effects of the pallidal lesions remain to be elucidated. In particular, it is of interest to determine to what extent these effects stem from the actual reduction of the size of striatal lesion and/or reflect GP lesion-induced effects on the functioning of basal ganglia–thalamocortical circuitry. However, given that similar dysfunction of the basal ganglia circuitry is thought to subserve the behavioral alterations seen in QA lesioned rats and HD patients, the present results raise the possibility that lesions to the GPe could ameliorate some of HD symptoms, similarly to ameliorating effects of lesions to the internal segment of the GP in Parkinson's disease [33]. Interestingly, there is some evidence that stereotaxic pallidal lesions can ameliorate hyperkinetic movements in affected patients [34,35]. Moreover, the present results raise the possibility that GPe lesion in the early stages of the disease would slow down the progressive degeneration of the striatum.

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