Effects of STN lesions on simple vs choice reaction time tasks in the rat: preserved motor readiness, but impaired response selection

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Abstract

The subthalamic nucleus (STN) is a key structure within the basal ganglia, inactivation of which is a current strategy for treating parkinsonism. We have previously shown that bilateral lesions of the STN or pharmacological inactivation of this structure in the rat induce multiple deficits in serial reaction time tasks. The aim of the present study was to investigate further a possible role for the STN in response preparatory processes by using simple (SRT) and choice (CRT) reaction time tasks. In contrast to the CRT procedure, the information related to the location of where the response had to be made was given in advance in the SRT procedure. Accurate performance on these tasks requires not only the selection of the correct response (i.e. which response), but also preparation in order to perform when required. A comparison between the two tasks allows assessment of whether STN lesions affect which response (‘which’) or when to perform it (‘when’). As previously observed in these procedures, the responses were faster as a function of the variable foreperiod preceding the trigger stimulus. This well-known effect, termed ‘motor readiness’, was maintained after STN lesions, suggesting that STN lesions did not affect the ‘when’ phase of action preparation. However, while performance on the SRT was faster than on the CRT task preoperatively, STN lesions slowed RTs and abolished the beneficial effect of advance information, suggesting a deficit in the selection (‘which’) phase of response preparation. This deficit in the selection phase was further supported by deficits in accuracy of responding after STN lesions, as well as increases in mislocated premature responding in the SRT condition. Together, these results suggest that the STN plays an important role in response preparatory processes, including response selection and inhibitory control processes.

Introduction

A crucial role for the subthalamic nucleus (STN) within the basal ganglia has recently been proposed by virtue of its ‘pace-making’ interactions with the globus pallidus (Plenz & Kitai, 1999; Wichmann & DeLong, 1999; Magill et al. 2000). However, the role of the STN in normal and pathological functioning remains unclear. Lesions of the STN induce obvious motor impairments (Whittier, 1947; Whittier & Mettler, 1949). Moreover, lesioning or inactivation of the STN ameliorates some of the motor symptoms of dopamine depletion (including Parkinson’s disease; Bergman et al., 1990; Aziz et al., 1991; Benazzouz et al., 1993; Baunez et al., 1995a; Limousin et al., 1995; Gross et al., 1999; Henderson et al., 1999; Phillips & Brown, 1999). However, the possible involvement of the STN in attentional functions has only recently been addressed (Baunez et al., 1995a; Baunez & Robbins, 1997, 1999).

The STN is a critical nexus in two of the three main routes by which corticolimbic information can reach basal ganglia output structures [i.e. the internal pallidum (GPi) and substantia nigra pars reticulata (SNr)]. The STN processes cortico-striatal information via the external pallidum (globus pallidus, GP, on the so-called ‘indirect pathway’) and it receives fast excitatory projections from wide regions of the cerebral cortex (Kitai & Deniau, 1981; Ryan & Clark, 1991; Nambu et al. 2000). The STN itself also has fast excitatory projections to the output structures (GPi and SNr). Cortical signals may thus reach these output nuclei via the STN prior to the arrival of synchronized signals traversing the direct and indirect pathways. As the cortico-STN-output nuclei pathway has a net excitatory effect, it opposes net inhibition from the cortico-striatal-output nuclei pathway and, thus, presumably modulates or shapes response output.

The present study analysed effects of STN lesions on several aspects of response preparatory processes essential for the normal selection of behavioural responses to specific environmental stimuli. These preparatory processes include the advance selection and programming of a specific action (‘which’), and ‘when’ to perform it (including the process of response set or ‘motor readiness’). We have, therefore, compared the effects of STN lesions in rats trained on two different reaction time tasks: simple reaction time (SRT) with advance information and an uncued choice reaction time (CRT) task,
employed by Brown & Robbins (1991) to examine the effects of unilateral striatal dopamine (DA) depletion. The advanced provision of information in the cued SRT (as distinct from the CRT) task allows the animal to prepare the response in advance of the imperative signal and maintain (or hold ‘on-line’ in working memory) the selected response in a hypothetical buffer store. A comparison of performance in these two tasks after STN lesions thus allows analysis of possible deficits in response preparatory processes, postulated by those recent computational models of the basal ganglia that give the STN a role in response selection (Houk & Wise, 1995; Mink, 1996; Berns & Sejnowski, 1998; Redgrave et al., 1999). Specifically, we aimed to test the hypothesis that the fast cortico-STN-output nuclei pathway helps to erase or nullify the effect of the immediately prior response, thus, facilitating performance of the currently selected action.

Materials and methods

Animals
Male Lister hooded rats (Charles River, UK; \( n = 38 \)) were housed in pairs and maintained on a 12-h light : 12-h dark cycle (lights on at 0700 h). During the experiment they were kept at 85% of their free feeding weight by restricting their food to 15±17 gm per rat per day. Water was provided ad libitum, except during experimental sessions. All procedures were conducted in accordance with the requirements of the UK Animals (Scientific Procedures) Act 1986.

Apparatus
Eight 25 × 25 cm aluminium nine-hole boxes, built in the Department of Experimental Psychology, University of Cambridge, were used. These boxes had nine 2.5 cm square holes with an infrared photocell beam crossing the entrance vertically on the curved rear wall. This latter wall was curved so that the distance between the magazine and each hole could be equal (25 cm). The photocell beam was located so that the nose-poke could be detected very early, minimizing the interval between initiation of a nose-poke withdrawal and detection of this withdrawal. Each hole was equipped with a green LED providing possible illumination from the rear. Only three holes were used [holes four to six (from the left hand side)], the others were blocked by a metal cap. At the front of the chamber, a magazine connected with a food pellet dispenser to which the rat gained access by pushing a Perspex® panel, monitored by a microswitch. The apparatus and on-line data collection was controlled by an Archimedes computer system running ARACHNID software (Paul Fray Ltd, Cambridge, UK) written by T. Humby.

Behavioural tests

Simple reaction time (SRT)
One group of rats (\( n = 18 \)) was trained to perform a simple reaction time task with an advance informative cue (see Fig. 1), adapted from the task previously described to test the effects of dopamine depletion in the striatum (Brown & Robbins, 1991). The animals were trained to start a trial by poking with their nose in the central hole (hole five) when the lights at the rear of the holes were at intermediate levels of brightness. Simultaneously, the level of brightness was modified in holes four and six; either to a brighter or dimmer level of brightness, giving information as to which side to respond. About half of the animals were trained with the rule: ‘bright go right and dim go left’ and vice versa for the other half. They had then to sustain their nose poke until the occurrence of a tone trigger stimulus to make their response, which was a nose poke in either the right (i.e. hole six) or the left (i.e. hole four) hole. The occurrence of this stimulus was randomly distributed within four various foreperiods (0.5, 0.75, 1.0 and 1.25 s). The level of brightness specifying the location of the response was returned to intermediate 0.3 s before the tone in order to force the rats to prepare a response and maintain it in the response buffer (a form of working memory). Otherwise it has been observed that rats tend to wait longer to initiate their response and fail to exhibit faster RTs relative to the CRT condition that reflect the advance information provided (VJ Brown and TW Robbins, unpublished observations).
Choice reaction time (CRT)

The second group of rats (n = 20) was trained to perform a two choice reaction time task (see Fig. 1). In this task, the beginning of the trial was similar to the SRT task, but the intermediate level of brightness remained until tone onset. The brightness level changed simultaneously with the onset of the tone and remained on until the withdrawal of the nose from the central hole [reaction time (RT)], to move back to intermediate level. The occurrence of the tone was randomly distributed within four foreperiods (0.5, 0.75, 1.0 and 1.25 s). About half of the animals were trained with the rule: ‘bright go right, and dim go left’, while the other half learned the opposite rule.

A single nose poke response in the appropriate hole was taken to be a ‘correct response’ and rewarded by the delivery of a food pellet, whereas, a nose poke in the other hole was recorded as an ‘incorrect response’. Additional responses in any hole were recorded as ‘perseverative responses’. Withdrawals of the nose from the central hole before the tone were recorded as ‘early withdrawals’, while responses in either holes four or six during this period were recorded as ‘premature responses’. Both incorrect and premature responses were punished by a period of darkness (‘time out’). Additional nose poke responses performed during the time out periods were recorded. For premature responses and early withdrawals, the trial counter was not increased and the same trial was restarted until a correct, incorrect response or omission was made. When no response was made within 5 s., an ‘omission’ was recorded.

The RT was taken to be the time elapsing between the onset of the tone and the withdrawal of the nose from the central hole, while the movement time (MT) was the time recorded between the withdrawal of the nose from the central hole and the nose poke in the response hole. Both measures were recorded for both correct and incorrect responses. RTs below 90 ms were discarded from the analysis, as they are more likely to be premature responses.

The number of presses on the panel of the food magazine was also recorded, as well as the latency to collect the reward. Premature responses immediately following a correct trial were also analysed to study possible effects of proactive interference of this former trial on response choice in the CRT condition. Furthermore, when the animals made a premature response, the accuracy in location of the response was analysed regarding the current stimulus presented to the rat, while the withdrawal of the nose from the central hole and the nose poke in the response hole were recorded as ‘premature responses’.

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Rats reached the criterion of preoperative stability of performance when they performed at least 80% correct responses over six consecutive sessions.

Statistical analysis

The data were analysed using the Clear Lake Research analysis of variance (CLR ANOVA) or Statview 5 programs. The results are expressed as means for each of the variables (i.e. accuracy, incorrect responses, premature responses, omissions, correct and incorrect RTs) per block of six sessions in the four different groups of animals.

For each variable, the data were submitted to mixed design ANOVAs with group (sham vs STN lesions) and task (simple vs choice) as the between-subject factors, the blocks of six sessions [(A) one block presurgery; four blocks postSTN lesion; (B) days 10–15 postlesion; (C) days 16–21 postlesion; (D) days 22–27 postlesion and (E) days 28–33 postlesion] and the foreperiods as the within-subject factors, when appropriate. When significant effects were found, post hoc comparisons between means were made either for preoperative block or for postoperative sessions, between groups or tasks, using simple main effects analysis and Newman–Keuls tests as appropriate.

To further investigate the location of premature responses with regard to the just-rewarded side, a one-level X^2 value was calculated to compare the percentages of premature responses located to the same side with a theoretical 50% location. For this latter analysis, SRT and CRT conditions were collapsed.

Surgery

All the animals were anaesthetized with xylazine (15 mg/kg, i.m.) and ketamine (100 mg/kg, i.m.) and secured in a Kopf stereotaxic apparatus. Twenty-one rats received bilateral injections of ibotenic acid (RBI; 9.4 μg/μL, i.e. 53 nmol) and 17 rats received the vehicle alone [phosphate buffer saline (PBS) 0.1 M]. The volume injected was 0.5 μL per side infused over 3 min using a 10-μL Hamilton microsyringe, connected by Tygon tubing fitted to the 30-gauge stainless steel injector needles, and fixed on a micropump calibrated to deliver the exact volume in the period of 3 min.

The injection coordinates were taken as the average of interaural and bregma coordinates from the atlas of Paxinos & Watson (1986): from the bregma: AP, −3.8 mm; L, +2.4 mm; DV, −8.35 mm (from skull) and from the interaural point: AP, +5.2 mm; L, +2.4 mm; DV, +1.65 mm, incisor bar set at −3 mm. Protection of the paws from self-biting was provided by bandaging and i.p. injection of Valium (diazepam, 10 mg/kg, i.p.) was administered prior to recovery from anaesthesia to prevent convulsions.

Histology

After completion of the behavioural testing, all the animals were perfused under deep Euthatal anaesthesia with PBS followed by 4% paraformaldehyde (PFA) solution through the left cardiac ventricle. The brains were removed and then either put into 20% sucrose solution overnight, to be cut with a microtome, or kept in PFA to be cut with a vibratome. The 60-μm-thick sections were stained with cresyl violet to detect the extent and location of the lesions.

Results

Histology

The extents, in individual cases, of the bilateral ibotenic lesions of the STN were determined after examination of brain slices at the level of the STN in all rats. As compared to sham control animals, the lesioned rats showed gliosis and loss of neurons within the STN (Fig. 2A and B). No spared neurons were found in the medial part of the STN, although some neurons remained in the lateral part in almost all the animals. The extent of the lesion is shown on Fig. 2C. Almost all the animals. The extent of the lesion is shown on Fig. 2C. Although STN lesions induced a shrinkage of the structure that appeared to have lost its ‘drop-like shape’, no damage was observed in the surrounding structures. Eight animals belonging to the lesion group (n = 2 in SRT group and n = 6 in CRT group) had inappropriate lesions that were located dorsally to the STN into the zona incerta and the thalamus and were discarded from the results analysis. The resulting n in each group was: SRT Sham, n = 9; SRT STN, n = 7; CRT Sham, n = 8 and CRT STN, n = 5.

Behavioural results

Pre-operative performance

Pre-operative performance was compared in the SRT and CRT conditions, but the rats were also divided into groups receiving future

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STN or sham surgery, to check that performance was matched in the main task variables across the to-be-operated groups.

As illustrated in Fig. 3, overall, RTs were significantly longer in the CRT condition, confirming the benefit of advance information given in the SRT condition ($F_{1,25} = 5.29, P < 0.05$). In both SRT and CRT conditions, RT decreased as a function of foreperiods, with faster RTs at the longer foreperiod ($F_{3,75} = 22.39, 15.39, P < 0.05$), indicating a ‘motor readiness effect’.

Neither RTs for incorrect responses nor MTs differed across SRT vs CRT conditions in the to-be-operated groups ($F_{1,25} = 0.02$ and 0.002, respectively, $P > 0.05$, not illustrated), MTs for correct responses before surgery ($F_{1,25} = 0.96$, all $P > 0.05$).

As shown in Figs 4 and 5, the to-be-operated groups were matched prior to surgery in task performance in terms of both accuracy and premature responses.

**Effects of STN lesions on SRT/CRT**

**Reaction time and ‘motor readiness’**

Figure 3 shows mean RTs for SRT and CRT before, (block A) and after surgery (only block B shown), plotted as a function of the foreperiods. In block B, although RT was lengthened in all groups, it was significantly increased in STN lesioned rats ($F_{1,25} = 7.63, P < 0.05$). The effect was so strong for rats trained in the SRT condition that there was no longer a significant difference between SRT and CRT in lesioned groups ($F_{1,25} = 0.01, P > 0.05$), indicating that the STN lesioned animals in the SRT condition no longer showed any benefit of advance information.

The ‘motor readiness effect’ was maintained after STN lesions ($F_{3,75} = 14.49, P < 0.01$).

RTs for incorrect responses also increased after STN lesions ($F_{1,25} = 4.38, P < 0.05$). STN operated rats were significantly slower in SRT than CRT conditions throughout blocks B–E ($F_{1,25} = 7.79, 11.31, 7.71$ and $18.36$ respectively, $P < 0.05$).

**Movement time (MT)**

There was no significant difference between SRT and CRT conditions for MT after surgery ($F_{1,25} = 3.97, P > 0.05$), nor between sham control and lesion animals for the four various postoperative blocks ($F_{1,25} = 3.71, 0.04, 0.19$ and $0.75$, respectively, $P > 0.05$, data not shown).

Fig. 2. (A and B) Structural damage induced by STN ibotenic acid-induced lesions. Photomicrographs of sections stained with cresyl violet, at the level of the STN outlined by dotted lines, in a sham control animal (A) and in a lesioned animal (B). (C) Reconstruction of coronal sections (from Paxinos & Watson, 1986) indicating the smallest (grey area) and largest (black area) extent of the lesions induced by bilateral injection of ibotenate (9.4 mg/mL, 0.5 µL/side) in the STN. Gliosis and cell loss were found in the anterior planes extending from −3.6 mm to −4.3 mm from bregma according to the atlas. Scale bar, 100 µm (A and B).
Accuracy

As illustrated in Fig. 4, STN lesions impaired the accuracy of responding when compared to control sham-operated animals ($F_{1,25} = 12.59, P < 0.01$). Although animals performing in the SRT task seemed to be more severely impaired than those in the CRT condition in terms of accuracy, there was no significant difference between SRT and CRT conditions ($F_{1,25} = 0.88, P > 0.05$).

Premature responses

As shown in Fig. 5, STN lesions significantly increased premature responding for both SRT and CRT conditions ($F_{1,25} = 18.04, P < 0.01$), the deficit was long-lasting (over the four post-surgery blocks of sessions, i.e., 33 days post-lesion) ($F_{1,25} = 19.52, P < 0.01$).
SRT (circles) and CRT (squares) as a function of blocks of six sessions: = 7 and STN Choice, the same location as the just rewarded response. Results are illustrated for response preparatory processes. Movement time was unaffected, behaviour, perhaps related to the human `inhibition of return' phenomenon (Rafal & Robertson, 1995). This was the case regardless of SRT or CRT condition; this was interpreted by those authors as reflecting an impairment in the general readiness to respond rather than an effect on programming of specific responses. By contrast, STN lesions did not impair the 'speeding' of responding as a function of the foreperiod in the SRT or CRT conditions, suggesting that the readiness to respond was unaffected after STN lesions. It thus seems that the STN might not be critically involved in the 'when' phase of preparation of action. Although it could be argued that premature responses suggest a deficit in 'when' processes, they could more likely result from general disinhibition. The involvement of striatal dopamine, but not STN, in 'motor readiness' perhaps indicates a critical role for the direct pathway (striatum–GPi/SNr) in this process.

As the brightness level was returned to an intermediate level 300 ms before the imperative tone in the SRT condition, this precue offset could have been used as a 'trigger' for responding, which could thus have been responsible for the faster RTs observed in that condition. However, had the gap been used as a cue, that would have led to the abolition or attenuation of the 'motor readiness effect', which did not occur.

Discussion

The present study has shown a number of deficits in the control of reaction time performance that help us to define the normal functions of the STN. Bilateral STN lesions did not affect the ability to exhibit speeding of RT as a function of the foreperiod preceding the imperative stimulus (i.e. intact 'motor readiness'), contrasting with the effects of striatal DA depletion (Brown & Robbins, 1991), and, thus, showing the specificity of the effects on some aspects of response preparatory processes. Movement time was unaffected, showing an absence of global motor impairment. However, the lesioned animals trained in the SRT condition lost the benefit of advance information, as shown by a lengthened RT that became as slow as that exhibited by animals trained in the CRT condition. Furthermore, STN lesions impaired choice accuracy in both the SRT and CRT conditions. The lesions also impaired response control, as shown by increased premature responding. This impulsive responding in STN-lesioned rats was also mislocated (i.e. was directed to the noncued location) in the SRT condition, where advanced information was provided about the correct response. STN lesions also induced proactive interference, as expressed by perseverative responses on the same side of the just-rewarded trial.

Those animals discarded from the behavioural analysis because of misplaced lesions exhibited different patterns of behaviour than rats with accurate bilateral STN lesions, showing only slight deficits when the lesions were either located in the STN but were only restricted to a very small portion of the nucleus or were asymmetric. Rats showed no deficit at all when lesions were located above the STN in the zona incerta. These observations suggest that the deficits described are specifically related to bilateral damage of the STN.

**STN lesions do not impair ‘motor readiness’ (‘when’ to respond)**

The normal ‘speeding’ of responding, that occurs with the lengthening of the foreperiod prior to the imperative signal in both CRT and SRT, is an index of ‘motor readiness’, reflecting some aspect of motor preparation, as previously described in several species (Macar et al., 1973; Näätänen & Merisalo, 1977; Frith & Done, 1986; Brown & Robbins, 1991; Baunez et al., 1995b). Such ‘speeding’ was abolished by striatal DA depletion (Brown & Robbins, 1991) regardless of SRT or CRT condition; this was interpreted by those authors as reflecting an impairment in the general readiness to respond rather than an effect on programming of specific responses. By contrast, STN lesions did not impair the ‘speeding’ of responding as a function of the foreperiod in the SRT or CRT conditions, suggesting that the readiness to respond was unaffected after STN lesions. It thus seems that the STN might not be critically involved in the ‘when’ phase of preparation of action. Although it could be argued that premature responses suggest a deficit in ‘when’ processes, they could more likely result from general disinhibition. The involvement of striatal dopamine, but not STN, in ‘motor readiness’ perhaps indicates a critical role for the direct pathway (striatum–GPi/SNr) in this process.

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**STN lesions impair response selection (‘which’ action)**

Comparison between the SRT and CRT conditions allows inferences about response preparatory processes (Pullman et al., 1988; Brown & Robbins, 1991; Jahanshahi et al., 1992). When information was given in advance (i.e. SRT condition), performance was enhanced with RTs being faster, thus, demonstrating the benefit of advance information. STN lesions completely abolished this beneficial use of advance information. Although there was no significant difference between sham and lesioned animals in the CRT condition due to a substantial RT increase in the sham group, RTs were longer in both SRT and CRT conditions. This suggests that STN-lesioned rats failed to
impaired response selection.

responses, often leading to the production of apparent `speeding' may have been biased by the low number of trials shown that bilateral STN lesions induced faster RTs. However, this a competition between the two possible when R2 should be stored there. There is, thus, a competition between the two possible responses, often leading to the production of the just-rewarded response (R1) and an impaired response selection.

A third possible explanation for a deficit in choice accuracy is attentional in nature (Baunez & Robbins, 1997), possibly resulting in decreased choice accuracy and increased premature responding in the SRT condition. The attentional load of the present task was, however, minimized by bilateral cue presentation, which reduced the need to orientate to the stimuli.

These three hypotheses additionally suppose that the selection of an incorrect response results from deficits in stimulus registration, encoding or retrieval. However, it seems most likely that the STN is implicated in the selection of motor actions, as predicted by recent computational models of basal ganglia (e.g. Redgrave et al., 1999).

**STN lesions may impair the operation of a ‘response buffer’**

STN lesions were postulated to impair the operation of a ‘buffer-like’ mechanism (a ‘motor’ working memory) which holds a selected response in readiness for performance until the appropriate imperative signal, and which would have to be reset (or ‘cleared’) after performance to allow subsequent responding; this is illustrated in Fig. 8. In addition to the deficit in response selection described above, STN-lesioned rats appeared to be impaired in the operation of this buffer, not only (i) by increases in premature responses that occur prior to the imperative signal, but also (ii) by an increased effect of proactive interference from the previously reinforced response that leads to a failure to ‘reset’ the buffer. These specific deficits in preparatory responses contrast with the sparing of more general ‘motor readiness’, required for appropriate changes in posture to facilitate responding when the imperative signal occurs (see Brown & Robbins, 1991).

In the present study, sham-operated control rats alternated from the just-rewarded response when they made a premature response, consistent with the normal tendency for rats to exhibit variation in their reinforced spatial responses (e.g. Olton, 1979), and possibly consistent with ‘inhibition of return’ phenomenon in humans (Rafal & Robertson, 1995). In contrast, STN-lesioned animals tended to perseverate on the just-rewarded trial when making a premature response, especially when trained on the CRT procedure. This result suggests, in support of the hypothesis, that the STN normally plays a

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**Fig. 8. Schematic representation of the ‘buffer hypothesis’.**

Top, when response 1 (R1) has to be executed, it is planned, stored in the ‘buffer store’ and, thus, initiated, leading to reward. Middle, in normal conditions, when a second response (R2) has to be executed, it also has to be planned and stored in the buffer, but this latter buffer contains the former response. Clearing of the buffer store has to be made; hypothetically controlled by an influence of STN. When R1 is cleared from the buffer, R2 can be stored and then produced. Bottom, in cases of STN lesions, the buffer cannot be cleared and R1 remains in the buffer store when R2 should be stored there. There is, thus, a competition between the two possible responses, often leading to the production of the just-rewarded response (R1) and an impaired response selection.

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**Response 1 (R1)**

"Limited capacity response buffer"

Production of R1 — Reward

**Response 2 (R2)**

"Limited capacity response buffer"

R2 — R1 — Production of R2 — Reward

**Normal condition**

**STN influence**

Clearing the buffer (R1 out)

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**Response 2 (R2)**

"Limited capacity response buffer"

R2 — R1 competition

Production of R1 — Time-out

Failure to clear buffer (R1 stays in)

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**Effects of STN lesion**

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role in protection from proactive interference arising from just-reinforced responses, by clearing the buffer as illustrated in Fig. 8.

STN lesions induced effects different from those described after unilateral dopamine depletion of the dorsal striatum (Brown & Robbins, 1991). Striatal DA depletion disturbed readiness but preserved response programming (i.e. accuracy remained intact). In contrast, we have shown severely impaired accuracy of responding in STN-lesioned rats with a preservation of ‘motor readiness’. This double dissociation of deficits suggests a differential involvement of the two systems, within the basal ganglia, in processes controlling response selection and preparation. According to this view, cortico-striatal and cortical–STN projections contribute to response selection, whereas, the readiness to perform the correct response depends upon dopaminergic modulation, possibly of the direct pathway.

The present study has, thus, revealed a critical role for STN in two distinct aspects of response preparation: (i) enabling the use of advance information (ii) preventing response interference, both aspects requiring intact response selection and ‘motor’ working memory processes. These functions confirm the critical position of the STN in the neural circuitry controlling the selection and initiation of voluntary, goal directed actions.

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Abbreviations

CRT, choice reaction time; GP, globus pallidus; GPI, internal pallidum; i.m., intramuscular; i.p., intraperitoneal; MT, movement time; PBS, phosphate buffer saline; PFA, paraformaldehyde; RT, reaction time; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; SRT, simple reaction time.

References


