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Motivational vs. Motor Effects of Striatal and Pallidal Gabergic Projections to Subthalamic and Entopeduncular Nuclei, Ventromedial Thalamus, and Ventral Globus Pallidus[1,2]

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WILLIAMS, S. F. AND L. J. HERBERG. *Motivational vs. motor effects of striatal and pallidal gabergic projections to subthalamic and entopeduncular nuclei, ventromedial thalamus, and ventral globus pallidus.* PHARMACOL BIOCHEM BEHAV **26**(1) 49–55, 1987.—Four GABA-terminal sites downstream from the rat corpus striatum were injected bilaterally with either a GABA agonist (muscimol 15–250 ng) or antagonist (picrotoxin 15–300 ng), and the effects on spontaneous locomotor activity or variable-interval hypothalamic self-stimulation were recorded. Significant changes in locomotor activity were produced at all four sites, as in previous studies. Two of the sites tested, the anterior globus pallidus and the thalamic ventromedial nucleus, also receive gabergic projections from the nucleus accumbens or from structures other than the basal ganglia; at these two sites, injection of either muscimol (depressant), or picrotoxin (facilitatory), had the same effect on self-stimulation as on locomotor activity. The two other sites tested, the entopeduncular nucleus and subthalamic nucleus, do not receive projections from the accumbens; in these two structures, muscimol enhanced locomotor activity but abolished self-stimulation; picrotoxin was without significant effect, or was disruptive. These results confirm previous reports that gabergic systems downstream from the striatum can mediate a simple, innate motor sequence (locomotion), but they fail to demonstrate a specific involvement of these pathways in learned behaviour (self-stimulation).

Basal ganglia Catalepsy Dopamine Entopeduncular nucleus GABA Globus pallidus Hypothalamus Intracranial injection Locomotor activity Motivation Muscimol Pallidum Picrotoxin Self-stimulation Stereotypy Striatum Subthalamic nucleus Thalamic ventromedial nucleus

CONTROL of posture and certain types of movement by brain dopamine (DA) has been shown to depend critically on a system of GABA-containing pathways, efferent from DA terminals in the corpus striatum [7, 12, 14, 49, 58]. Delineation of these pathways is incomplete, but a simplified schema (for the rat) is given in Fig. 1.

Injection of GABA-mimetic agents into sites in Fig. 1 containing the terminals of striatal gabergic neurons generally evokes typical dopaminergic effects, including heightened general activity, circling and certain stereotyped movements [3, 8, 29, 47, 48]. The opposite picture, culminating in catalepsy, has been elicited from other GABA terminal sites, in some cases known to be separated from the striatum by an additional sign-inverting (inhibitory) synapse [11,44]. The DA-like effects appear to be initiated downstream from the dopaminergic system since they are not abolished by pretreatment with neuroleptic agents (reviewed by Di Chiara and colleagues [12] and Scheel-Krüger and colleagues [49]).

A question of considerable interest is whether the gabergic outflow from the basal ganglia contributes to higher-order functions such as learning and the various forms of motivated behaviour in which DA is thought to play

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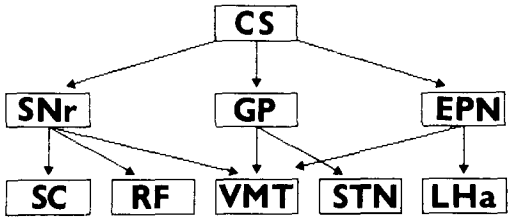

FIG. 1. Gabergic pathways, acted on by dopamine (directly, or via an interneurone [35]), run from the striatum (CS) to the substantia nigra pars reticulata (SNr) [3, 13, 16, 40], to the entopeduncular nucleus (EPN) [16, 20, 48] and to the globus pallidus (GP) [16, 20, 44]. They relay at these three sites via a second gabergic neuron to at least five destinations, including the ventromedial thalamus and associated nuclei (VMT) [5, 11, 29, 58], the superior colliculus (SC) [2,6] and neighbouring reticular formation (RF) [47], the lateral habenula (LHa) [5,39] and the subthalamic nucleus (STN) [5, 8, 20, 48]. Other GABA-containing pathways, not shown, have been reported to run in the reverse direction (STN to GP and EPN, and GP to CS (see E. G. McGeer *et al.* [33,34]). The limbic system is linked by a projection from the nucleus accumbens to the GP [25,26]. Gabergic pathways from GP to EPN and SNr, and accumbens to SNr have been suggested, although the evidence for them has been questioned [5, 33, 40]. Other projections emanating from the striatum contain substance P [45], Met-enkephalin [52], and dynorphin [54].

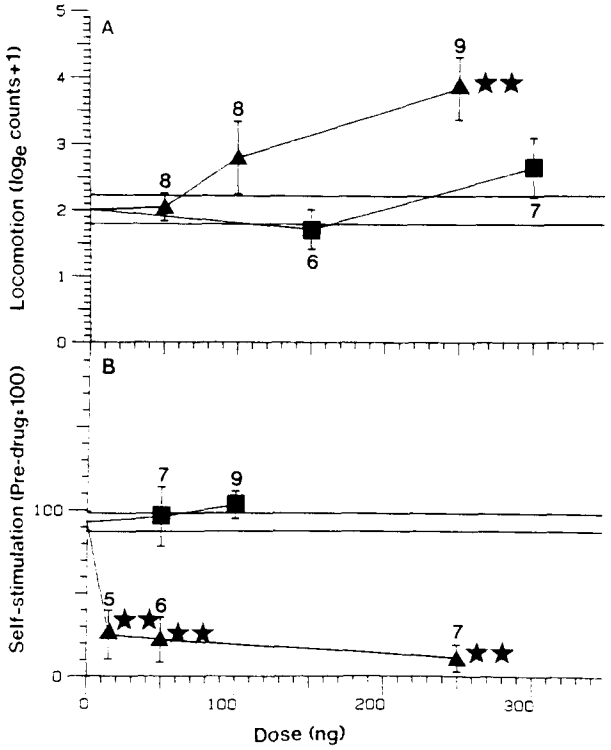

FIG. 2. Behaviour recorded 10–20 min after bilateral injections into the entopeduncular nucleus. Numerals indicate the number of rats. Vertical bars indicate standard errors. Paired horizontal lines indicate mean response rate ±SE, 10–20 min after injection of vehicle. A. *Locomotor activity:* effect of muscimol (▲) (ANOVA $p<0.01$), and picrotoxin (■) (ANOVA n.s.). B. *Self-stimulation:* effect of muscimol (▲) (ANOVA $p<0.01$), and picrotoxin (■) (ANOVA n.s.). ★$p<0.05$, ★★$p<0.01$.

an important part [24, 32, 57]. Only the nigrotectal projection has been systematically investigated in this respect: collicular lesions were found to block apomorphine-induced gnawing movements but not deprivation- or stimulation-induced feeding, and were also without effect on other indices of motivational arousal [9,10]. The present study approached this question by examining the effects on behaviour of gabergic agonists and antagonists injected into four other GABA-terminal areas sited downstream from the DA terminals. Two specific behavioural measures were recorded: spontaneous locomotor activity, and the rate of variable-interval hypothalamic self-stimulation. Spontaneous locomotion is closely related to activity in mesolimbic DA pathways [28] and to current physiological state [18], though it is not necessarily indicative of general motivational arousal [56]. The neurochemical basis of self-stimulation remains obscure [50], but responding for submaximal currents at subcortical 'reward' sites is strongly affected by dopaminergic stimulants injected peripherally [53] or directly into DA-sensitive areas in the brain (including the striatum, but only its antero-ventral extremity, adjoining the nucleus accumbens [41]). In addition, DA D2-receptor blocking agents, such as haloperidol, inhibit self-stimulation in a dose-dependent manner at doses lower than are necessary to produce simple motor incapacity [17, 31, 55]. Thus self-stimulation provides a sensitive measure of the energizing role of DA in motivated behaviour [21], and response rates should accordingly detect any motivational effects of manipulating the downstream gabergic pathways.

METHOD

Subjects and Apparatus

Male Lister rats (Bantin & Kingman) weighing 215 to 280 g were housed individually with free access to food and water. Bilateral stainless steel 21-gauge guide cannulae and, in self-stimulation studies, twisted bipolar stainless steel electrodes (Plastic Products Co.), were implanted intracranially under anaesthesia produced with ketamine plus chlorpromazine. The electrodes were directed rostrally at an angle of 20° with respect to the vertical zero plane so as to clear the cannula projections. Electrode tips were aimed at a point in the mid-lateral hypothalamus traversed by mixed mesolimbic and nigrostriatal dopaminergic projections (de Groot coordinates A4.8, 1.3, 8.0) [46]. Guide cannulae were cut to length from hypodermic needles, and aimed at one of four sites: (i) the entopeduncular nuclei (EPN) (A5.4, ±4.0, 7.0, angled 10° medially to avoid traversing the ventricles); (ii) the subthalamic nuclei (STN) (A4.4, ±3.7, 8.0, angled 10° medially); (iii) the globus pallidus (GP) (A6.8, ±3.2, 6.5) and (iv) the thalamic ventromedial nuclei (VMT) (A5.0, ±1.4, 7.0). Solutions were injected through a 28-gauge internal cannula extending approximately 3 mm below the guide cannula. Placements were verified in enlarged photographic projections of 50-μm frozen sections, and patency and positioning of the cannulae were confirmed by the injection of 1 μl of a 2% aqueous solution of pontamine sky blue immediately after the rats had been killed. Test scores were incorporated in the final results only if both cannula tips were positioned within the relevant borders defined by the Pellegrino and Cushman atlas [46].

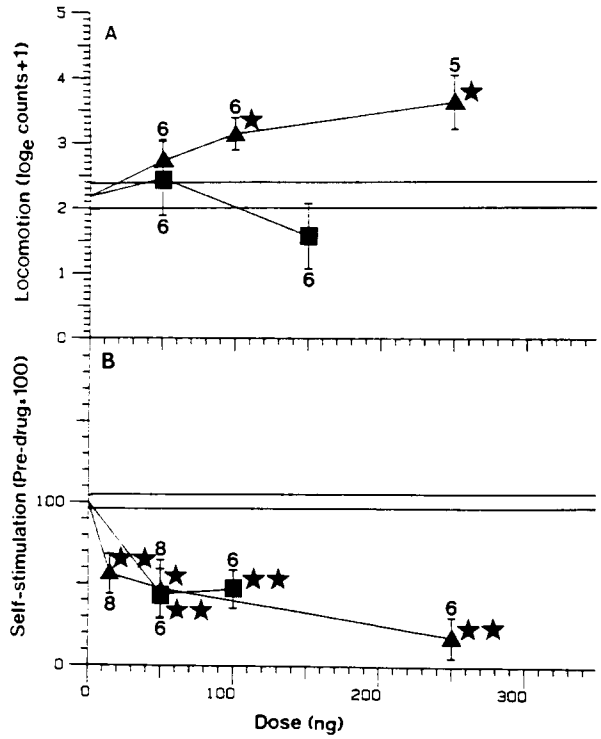

FIG. 3. Effect of injections into subthalamic nucleus. A. *Locomotor activity:* effects of muscimol ($p<0.01$) and picrotoxin (n.s.). B. *Self-stimulation:* effects of muscimol ($p<0.01$) and picrotoxin ($p<0.01$). Details as in Fig. 2.

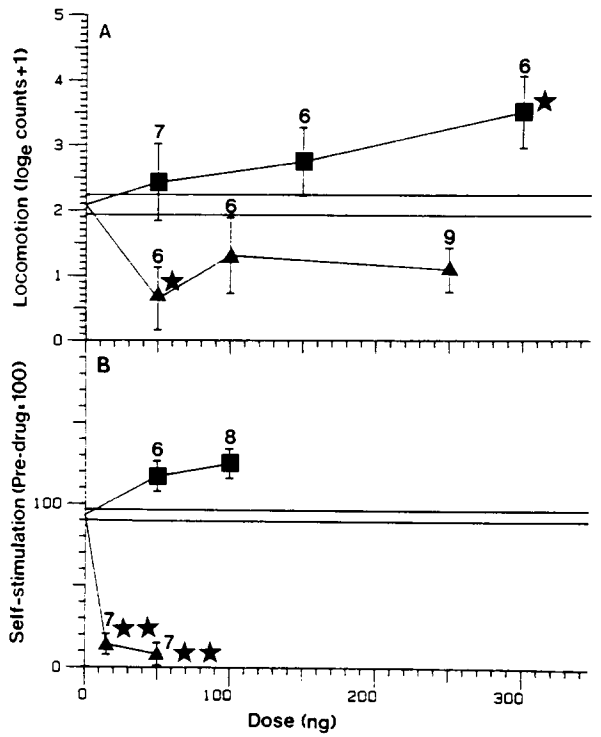

FIG. 4. Effect of injections into anterior globus pallidus. A. *Locomotor activity:* effects of muscimol ($p<0.05$) and picrotoxin ($p<0.01$). B. *Self-stimulation:* effects of muscimol ($p<0.01$) and picrotoxin ($p<0.05$). Details as in Fig. 2.

Self-Stimulation

Rats were trained to operate a pedal for a 0.5-sec 50-Hz reinforcing train available at randomly varied intervals of 10-sec mean duration; this schedule elicits a steady, seizure-free rate of responding well within the rat's maximal performance (see [22] for further details). The stimulating current was fixed at the lowest intensity that elicited sustained responding, and the rat's cumulated responses were recorded automatically at 5-min intervals. Drug effects were determined from the response rate recorded 10–20 min after injection, expressed as a percentage of the baseline rate recorded in the 30 min before injection. Scores obtained with each drug were analysed by means of a Kruskal-Wallis one-way analysis of variance. If analysis showed a significant dose-dependant effect on responding, response rates were compared with the corresponding rate after injection of vehicle by means of a Mann-Whitney *U*-test.

Locomotor Activity

Locomotor activity was measured in enclosed circular bowls 35 cm in diameter resting on a central pivot and six microswitches spaced about the perimeter. Counts made by movement of the rat from one part of the bowl to another were recorded automatically at 5-min intervals. Grooming or stereotyped postural movements without locomotion had no appreciable effect on the count [4], but rats making vigorous convulsive movements could not be accurately tested. Locomotor counts were normalised, for plotting, by log transform, and the effects of each drug were analysed by means of a Kruskal-Wallis analysis of variance. If significant overall, locomotor scores were compared to the corresponding score after injection of vehicle, by means of a Mann-Whitney *U*-test.

Procedure

Dose-response data for the effects of intracranial injections on locomotor activity and on self-stimulation were obtained for a representative GABA-receptor agonist, muscimol [15], and GABA antagonist, picrotoxin [1,51]. Separate groups of rats were used for the two behavioral tests. Injections were administered by means of a micrometer-driven microsyringe connected to the cannula by a short length of nylon tubing, the rat being held under light restraint. Injections were 1.0 μl in volume, given over a period of approximately 30 sec. The inner cannulae were then left in place for another 30 sec. Intracranial injections were given at intervals of not less than 48 hr, each rat receiving a maximum of four bilateral doses.

RESULTS

Entopeduncular Nucleus

Locomotor activity. Muscimol (250 ng) produced a significant increase in locomotor activity as compared to that recorded after saline (Fig. 2A); it also produced stereotyped licking and gnawing of surrounding objects, similar to that seen with high doses of apomorphine or amphetamine [28,32]. Picrotoxin did not affect locomotor activity over the

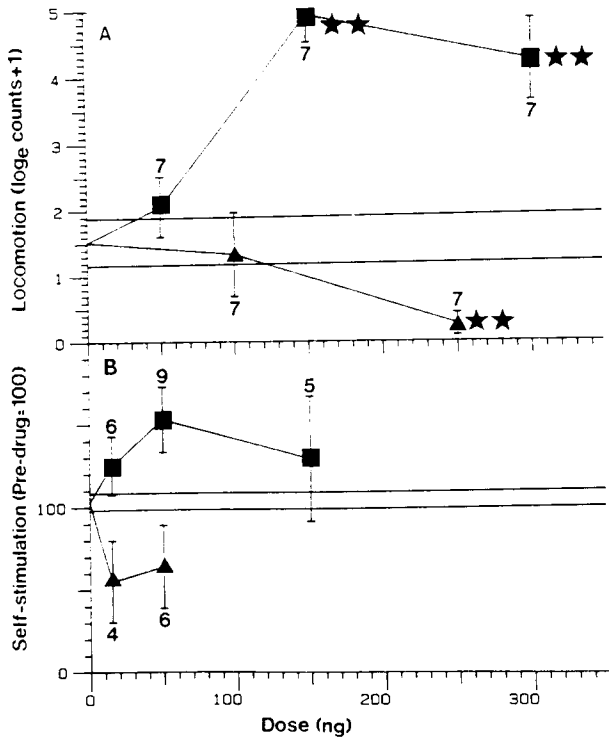

FIG. 5. Effect of injections into ventromedial thalamic nucleus. A. *Locomotor activity:* effects of muscimol ($p<0.01$) and picrotoxin ($p<0.01$). B. *Self-stimulation:* effects of muscimol ($p<0.01$) and picrotoxin ($p<0.05$). Details as in Fig. 2.

dose range tested; doses higher than 300 ng could not be tested because they tended to produce repeated myoclonic jerks, or convulsions.

Self-stimulation. The effect of EPN muscimol on self-stimulation (Fig. 2B) differed strikingly from its effect on locomotor activity. All doses caused a profound depression of self-stimulation, even doses that were much too low to affect locomotion (all doses being from the same batch and supplier). Picrotoxin was without significant effect in the dose range tested (Fig. 2B).

Subthalamic Nucleus

Locomotor activity. The effects of muscimol and picrotoxin in the STN (Fig. 3A) were similar to the effects obtained from the EPN. Muscimol (50–250 ng) again produced increased locomotion, interspersed with bouts of stereotyped activity, while picrotoxin (50–150 mg/kg) had little effect, apart from a transient catalepsy-like spell soon after injection.

Self-stimulation. Self-stimulation was strongly depressed by STN muscimol (Fig. 3B), though somewhat less strongly than it was by EPN muscimol. Response rates after a 15-ng dose in these two sites were respectively 50–60% and 15–20% of preinjection baselines. Stereotyped activity was again present, the act of lever pressing sometimes being incorporated into a short sequence of rearing and sniffing over a fixed path. Picrotoxin (50 and 100 ng) caused a similar depression of self-stimulation; none of the rats showed facilitation.

Globus Pallidus

Locomotor activity. Muscimol injected into the anterior part of the GP tended to depress spontaneous locomotor activity but this effect was not dose-related, being strongest at the lowest dose tested (50 ng, Fig. 4A). At this dose, the depressant effect was maximal after 20 min, followed 20 min later by a sustained rebound (not shown) to a level well above control scores (log counts/10 min = 3.6 ± 1.1 and 0.44 ± 0.27; $p<0.02$, for activity recorded 40–60 min after injection of muscimol and vehicle, respectively). Picrotoxin (300 ng) was followed by a prompt increase in locomotor activity (Fig. 4A), continuing without remission for at least 60 min. Lower doses had little effect.

Self-stimulation. Changes were in the same direction as the locomotor effects, but were much more marked. Muscimol (15 and 50 ng) virtually abolished responding, with no sign of rebound in the ensuing 60 min, while picrotoxin (50 and 100 ng) produced a significant enhancement (Fig. 4B).

Ventromedial Thalamic Nucleus

Muscimol depressed locomotor activity, though only at the highest dose (250 ng); picrotoxin coused strong facilitation (Fig. 5A).

Similar effects were produced on self-stimulation (Fig. 5B), though the depressant effect of muscimol was apparent at much lower dose-levels.

DISCUSSION

The purpose of this study was to see whether gabergic projections from the corpus striatum contributed not only to the control of posture and pre-programmed motor sequences such as locomotion [14], but also to a complex, acquired activity—operating a lever for brain-stimulation reward. Scheel-Krüger and colleagues [49] have suggested that the behavioural activation evoked by the local injection of muscimol or THIP into the EPN, STN or SNr shows such impressive similarity to the syndrome produced by stimulants such as apomorphine or amphetamine [28,32], that it seems likely that gabergic and dopaminergic agents produce these effects via the same mechanism. Hence, the injections of muscimol should also mimic the well-established effects of amphetamine on learned patterns of behaviour [32], including self-stimulation [21,53]. As appears below, this was found not to be the case.

Entopeduncular and Subthalamic Nuclei

The results confirmed previous reports [48] of increased locomotor activity, with stereotypy, after injection of muscimol into the EPN or STN. But the effects on self-stimulation were strongly in the opposite direction to the effect on locomotion; there was no enhancement of brain-stimulation reinforcement as would have been seen if muscimol were mimicking the locomotor stimulant action of dopamine. The suppression of self-stimulation could not have been caused by simple physical competition with stereotypic or locomotor movements elicited by muscimol, since suppression of self-stimulation was virtually complete with even the lowest dose tested (15 ng bilaterally); this dose of muscimol did not enhance locomotion, and had no discernible effect on behaviour other than on self-stimulation. Moreover, there is no evidence for any intrinsic incompatibility between locomotion and self-stimulation if each behaviour is measured independently (as they were here). The

two behaviours commonly show parallel changes with amphetamine and other stimulants [32,53] as they also did, in this study, with picrotoxin (Figs. 4 and 5). Thus the locomotor hyperactivity released by muscimol must differ in a fundamental way from the hyperactivity seen with amphetamine [32] and in other states of heightened motivational arousal [18].

The subconvulsive doses of picrotoxin tested on the EPN and STN failed to reproduce the sedative effects on locomotion seen by Scheel-Krüger and colleagues [48]. It is possible that a more precise titration of dose may have been needed.

Scheel-Krüger and Magelund [48] remarked that gabergic agents injected into the STN acted behaviourally in the same sense as in the EPN, even though the natural gabergic input into the STN is not direct from the striatum but is relayed to it via a sign-inverting synapse in the GP [14] (see Fig. 1). The present study confirmed Scheel-Krüger and Magelund's observation; the direction of the observed effect is perhaps explained by clinical [37] and anatomical [30] evidence indicating that the STN is not primarily an output station but instead provides a modulatory feedback service to the basal ganglia.

Globus Pallidus

Both locomotion and self-stimulation showed an initial increase after picrotoxin, and depression after muscimol. But the biphasic locomotor response to muscimol (depression, followed by hyperactivity), and the irregular dose-response relationship (seen in this and in previous studies [11, 44, 49]), show the GP to be a functionally non-homogeneous structure. Gabergic projections to the GP include fibres arising in the nucleus accumbens as well as the corpus striatum [25,26], and it has also been reported that injections of muscimol into sites in the GP situated more posteriorly are not cataleptogenic, or may even be uniformly stimulant [11,44]. Thus the effects of pallidal injections could reflect an action on overlapping or adjacent systems, and it is uncertain whether the effects on locomotion and self-stimulation were initiated by striatal efferents, or by other systems.

Ventromedial Thalamic Nucleus

The present results confirmed previous reports that bilateral injections of muscimol into the VMT depress locomotor activity and lead to catalepsy, with picrotoxin having the opposite effect [11,29]. Parallel results were obtained with self-stimulation: depression with muscimol, and facilitation with picrotoxin. These findings might suggest a motivational role for the striato-nigro-thalamic output route. Against this possibility is the finding of Di Chiara and colleagues [11] that muscimol injected into the ventral thalamus did not affect apomorphine-induced stereotyped behaviour, indicating that "striatal effects unrelated to posture . . . are conveyed by pathways independent of the thalamus" [11]. The question is further complicated by data indicating a high proportion of GABA terminals in the VMT to be situated on interneurons [29] or on projections from the thalamic reticular nucleus [5,29]. Thus the self-stimulation effects of the VMT, as of the GP, need not have involved a striatal output system.

GENERAL DISCUSSION

The results show that spontaneous locomotor activity and self-stimulation performance do not always vary in parallel. Locomotor activity, like certain other postural reflexes and activities such as breathing, defaecating and weeping, is an automatism organised by the basal ganglia [14,38]. Operant responses, like pressing a lever for brain-stimulation reward, depend more on arbitrary motor sequences which must be learned. The present results showed that gabergic pathways projecting to the GP and VMT may regulate (inhibit) both categories of behaviour, but the origin of these pathways is uncertain. Interconnexions between the basal ganglia are too intricate to allow of watertight distinctions, but the EPN and STN, as documented by Scheel-Kruger *et al.* [49], are devoid of input from the accumbens though receiving projections from "nearly the entire striatum and globus pallidus" [49]. Thus the relatively specific and selective action of these two structures may provide a clue to the possible functions of the striatum. In the present study, the EPN and STN facilitated locomotion, a quasi-reflexive operant, but not self-stimulation, an instrumentally reinforced operant, even though striatal output undoubtedly contributes to the coordination and automatic sequencing of motor programmes [19,36]. But sequencing of motor programmes may not have been relevant to the self-stimulation task; motor capacity or dexterity is unlikely to have been a limiting factor for the slow, easy variable-interval responding called for here. A more critical factor for low-level self-stimulation performance is the rat's motivational state. Responding at submaximal rates is ordinarily enhanced by conditions producing motivational arousal—whether by drugs, deprivation or tail-pinch [23, 27, 43]; thus it appears that injections of muscimol into the EPN or STN did not affect motivational state (except possibly, in a disruptive sense). Yet the same injections were shown to enhance locomotor behaviour. On this evidence, gabergic projections from striatum or GP to the EPN and STN may contribute to executive aspects of motor performance but not to the motivational processes that may underlie it [36,42].

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