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Behavioural Basis of the Dorsal Bundle Extinction Effect

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MASON, S. T. AND S. D. IVERSEN. *Behavioural basis of the dorsal bundle extinction effect.* PHARMAC. BIOCHEM. BEHAV. 7(4) 373–379, 1977. – Lesion to the fibres of the dorsal noradrenergic bundle arising from the locus coeruleus using the selective neurotoxin 6-hydroxydopamine has been shown to produce a resistance to extinction on a number of behavioural tests without affecting the acquisition learning process itself. The experiments reported here are aimed at elucidating the behavioural mechanisms involved in this resistance to extinction. Theories invoking general hyperactivity, internal inhibition and perseveration are tested in the following experiments and all are shown to be contrary to the observed facts. On the basis of other data it is tentatively concluded that the dorsal noradrenergic bundle may play a role in the filtering out of irrelevant stimuli or in the memory of non-reward.

Dorsal bundle | Locus coeruleus | 6-Hydroxydopamine | Locomotor activity | Frustrative nonreward | DRL | Perseveration | Internal inhibition | Noradrenaline

A ROLE for noradrenaline (NA) has been suggested in learning processes [9,17], with a specific NA pathway identified as the dorsal noradrenergic bundle arising from cell bodies in the locus coeruleus [21,45] and innervating wide areas of the cortex and limbic forebrain. The coeruleo-cortical [10,11] model of learning predicts that lesion to the locus coeruleus or the dorsal noradrenergic bundle should impair all types of learning [3], since the NA pathway is seen as a general reinforcement mediator, necessary for all types of long-term memories to be laid down. Direct tests of the coeruleo-cortical model of learning by lesion to the locus coeruleus or the fibres of the dorsal bundle have failed to implicate NA in learning in any general sense [1, 16, 25, 26, 27, 37, 39]. However, alterations in behaviour do occur after 6–OHDA lesion to the dorsal bundle in that these animals are resistant to extinction [25, 26, 27] and continue responding in the face of nonreward longer than controls. Resistance has been found in extinction of a food rewarded runway response [25], a CRF operant response [26, 43], a complex motor manipulative response [27], a go/no-go alteration task [44], in extinction of a fixed interval [28] and in extinction of a one-way [4] and a two-way [32] active avoidance paradigm.

The extinction effect cannot be due to a general learning impairment so other behavioural mechanisms will have to be postulated. The work reported here is designed to test some of these possibilities. One suggestion might be that the lesioned animals are simply hyperactive and so show increased responding in extinction. The simple hyperactivity mechanism would, of course, suggest that increased responding should be seen in acquisition as well, which is not the case. Nonetheless, an easy test of this hypothesis would be to measure the locomotor activity and open field activity of the lesioned rats. A second possibility, analogous to that suggested in the case of the resistance to extinction seen after surgical lesion to the hippocampus [14,18], might be that the dorsal bundle lesioned rats suffer from a deficit in internal inhibition and cannot withhold a response. It would be predicted that acquisition of a DRL (differential reinforcement of low rates of responding) schedule should be deficient in the lesioned rats. A similar mechanism has been suggested [34] to explain the reduced post-reinforcement pause found in NA depleted rats on a FR (fixed ratio) schedule.

A related but conceptually different mechanism might be a perseverative deficit. That is, although the lesioned rats have the capability to inhibit responding, they are slow to change from the previously prepotent response strategy when this is required. To test it would be necessary to establish a high rate of responding prior to DRL training (as immediate acquisition of a DRL task might not reveal a perseverative tendency on its own), which could be done by extended CRF training, amongst other ways.

METHOD

Catecholamine Depletion Techniques

Two different techniques for depleting cortical and hippocampal NA were used, the intracerebral injection of 6–OHDA into the fibres of the dorsal bundle in adult rats [25, 26, 27, 37] and the peripheral injection of 6-OHDA into the neonatal rat pup [7,42]. Recently the use of 6–OHDA has been questioned as to its specificity of action on catecholamine systems [5, 15, 20, 35]. Since even if the appropriate concentration and volume of 6–OHDA is used for intracerebral injection a very small region of nonspecific damage will occur at the tip of the cannula [40,46]. In

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order to control even for this small amount of nonspecific damage a second administration technique, the neonatal peripheral 6–OHDA was used [7, 26, 27, 42] which produces the same pattern of central catecholamine depletion but completely different nonspecific effects [33]. Thus, any behavioural effect common to these two preparations must be due to the only biochemical alteration present in both, namely the depletion of cortical and hippocampal NA. (For further discussion of this point see [27]).

Dorsal Bundle Technique (DB)

Male albino rats weighing approximately 200 g were anaesthetised with Equithesin (3 ml/kg), positioned in a Kopf stereotaxic apparatus, and the skull exposed. The head was levelled, two holes were drilled in the skull and a 30-gauge cannula lowered bilaterally to the following coordinates taken from Konig and Klippel [19] – 6 mm from bregma, 0.8 mm lateral from the midline and 5 mm below dura. In the case of the lesioned rats, 8 micrograms of 6–OHDA base dissolved in 2 μl of 0.9% saline with 1 mg/ml ascorbic acid antioxidant were infused at the rate of 1 microlitre per minute over 2 min; control animals received ascrobic-saline injection of the same volume but not containing any 6–OHDA. The cannula was left in place for a further 1 min to allow diffusion of the drug and then withdrawn and the skin sutured. The animals were then allowed two weeks recovery before behavioural testing commenced.

Neonatal Peripheral Technique (NPT)

Male albino rat pups were injected intraperitoneally with 100 mg/kg 6–OHDA base dissolved dissolved in 0.9% saline with 1 mg/ml ascorbic acid antidoxidant on Days 1, 3, 5, 7, 9 and 11 after birth. Controls received an equal volume of ascorbic-saline without any 6–OHDA dissolved in it. This method has been found [7,42] to produce effectively a lesion to the dorsal noradrenergic bundle since brain dopamine (DA) and hypothalamic NA are not affected. These animals do, however, have a permanent peripheral sympathectomy [7]. The animals were left to grow to maturity and behavioural testing started at three months of age.

Assay of Catecholamines

Following completion of behavioural testing the animals were sacrificed by decapitation and their brains assayed for NA and DA to confirm the adequacy and pattern of amine depletions obtained. The DB rats were sacrificed three months after surgery and the NPT rats six months after treatment, both groups thus being aged about six months at the time of assay. Following decapitation the brain was rapidly removed from the skull and dissected on ice into the following regions [27], cortex, hippocampus, hypothalamus, striatum, brainstem and cerebellum, which were then weighed and homogenized in 0.1 N perchloric acid. These homogenates were then assayed for NA and DA by a sensitive radioenzymatic method modified from Cuello, Hiley and Iversen [12] and Coyle and Henry [8]. This method is based on the conversion of catecholamines to their O-methyl derivatives in the presence of tritiated S-adenosyl methionine and the enzyme catechol O-methyl transferase.

EXPERIMENT 1

The internal inhibition hypothesis of the dorsal bundle extinction effect predicts an inability to withhold or inhibit a response if this is required by the behavioural task. A DRL schedule would be such a situation and the DB and NPT preparations were examined on the acquisition of this task in the following experiment. Locomotor activity tests of the hyperactivity explanation, in photocell cages and in an open field, are also briefly reported.

Animals

DB control n = 9, treated n = 9, NPT control n = 10, treated n = 10. Prior to DRL training all the DB and NPT animals, both treated and controls, had received identical training in a ball-in-the-tunnel situation, the details and results of which are reported elsewhere [27].

Behavioural Methods

DB and NPT animals were reduced to 90% of their free-feeding weight and fed 15 g of food per day after the operant test session. Water was available ad lib. Testing was carried out in Campden Instruments Skinner boxes, constructed of heavy duty aluminum with two levers projecting 1.6 cm from the front wall. Approximately 15 g force was required to depress either lever to produce contact closure and throughout this and the subsequent experiment the right lever was not in use and had no behavioural consequences. Reinforcement was delivered by an automatic feeder and was one 45 mg Noyes nutrient pellet. The schedule was programmed and data collected by an on-line computer (Computer Technology Ltd.). The animals were lever shaped by being given one ten-min session to explore the apparatus with the reinforcement tray overflowing with food pellets. On the next day a food pellet was delivered every time the animal inserted its head into the reinforcement tray. A fifteen-min session was allowed. On the next day food pellets were affixed to the left lever with Celophane tape and the feeder programmed to deliver one food pellet every time the lever was depressed (CRF). A 25 min session was given. At the end of this all animals had learned to lever press to some extent and were then placed for subsequent days onto the DRL 15 sec schedule. This meant that the animal had to wait for at least 15 sec after the last lever press before another lever press would be rewarded. A lever press before the 15 sec DRL interval had elapsed reset the time and so postponed reward. Sessions lasted 25 min and testing continued for 21 days. Three measures were recorded for each animal, the number of rewards obtained, the number of lever presses emitted and the percentage reinforced responses. The latter was calculated by dividing the number of rewards by the number of responses and multiplying by one hundred. Locomotor activity was measured both satiated and 24 hr food-deprived in photocell activity cages for 70 min for DB and NPT animals and in an open-field apparatus for 21 min for NPT animals.

Results

The number of reinforcements obtained by DB and NPT animals over the 21 days of DRL acquisition are shown in Fig. 1. At the end of the DRL acquisition period all animals had acquired the response pattern, were performing at about 35% and obtaining about 40 reinforcements per

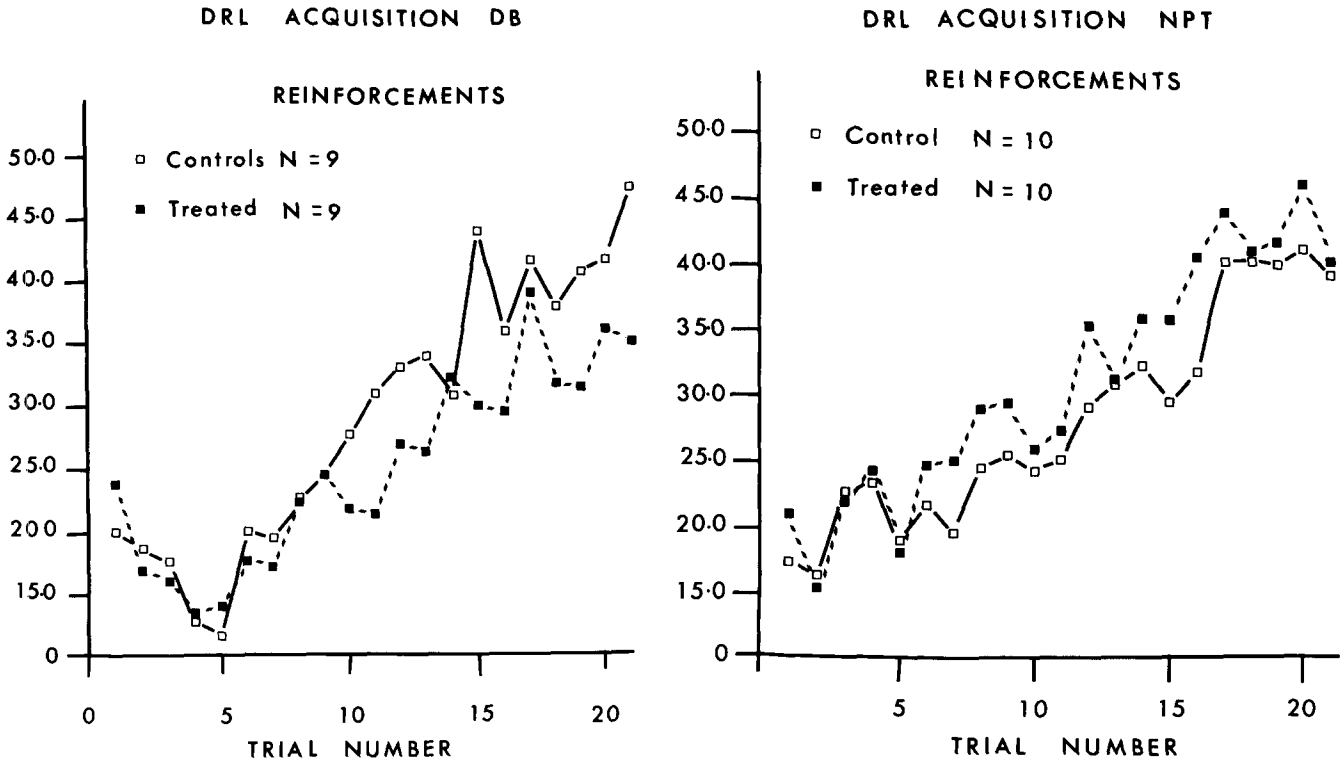

FIG. 1. Left: Mean number of reinforcements per session obtained by DB animals during the 21 sessions of DRL acquisition (without CRF pretraining). Right: As on left, but for NPT animals.

TABLE 1

DORSAL BUNDLE: VALUES ARE MEANS WITH STANDARD ERROR OF THE MEAN IN NG/GM WET WEIGHT OF TISSUE

	Control (n=9)	Treated (n=7)	%	*t* statistic
Noradrenaline				
Hippocampus	284 ± 72	53 ± 15	18.7	2.77*
Hypothalamus	796 ± 110	327 ± 86	41.1	3.20†
Cortex	252 ± 32	40 ± 12	16.2	5.57‡
Cerebellum	213 ± 20	171 ± 20	80.4	1.46
Dopamine				
Hypothalamus	351 ± 63	275 ± 27	78.4	1.00
Cortex	105 ± 21	73 ± 22	69.7	1.04
Striatum	5314 ± 673	7388 ± 808	139.0	1.98

Two treated animals in this group died between DRL testing and subsequent activity testing/biochemical assay.

The lower limit of accurate measure of noradrenaline for this and subsequent tables was 50 ng/gm tissue [26].

*Significant at 5% level
†Significant at 1% level
‡Significant at 0.1% level

session. Neither DB nor NPT rats showed any sign of slower acquisition than controls. Both lesioned groups were capable of inhibiting response emission over the 15 sec DRL interval to the same extent as their vehicle controls. A two factor analysis of variance with repeated measures on one factor, days, was carried out and showed no difference between the treated and control rats of either DB or NPT groups on any of the three measures of DRL performance. (All F ratios less than 1.0). No difference was found in baseline locomotor activity, either in the photocell activity cages or in the open-field for either the DB or NPT groups. (All F ratios less than 1.5.)

TABLE 2

NEONATAL PERIPHERAL TREATMENT: REGIONAL CONCENTRATIONS OF AMINES; VALUES ARE MEANS IN NANOGRAMS PER GRAM TISSUE WITH STANDARD ERROR OF THE MEAN

	Control (n=10)	Treated (n=10)	%	*t* statistic
Noradrenaline				
Hippocampus	374 ± 48	23 ± 6	6.2	7.2‡
Hypothalamus	756 ± 97	843 ± 146	112	0.49
Cortex	238 ± 24	6 ± 9	2.5	9.0‡
Cerebellum	247 ± 37	29 ± 26	11.7	4.8‡
Brainstem	185 ± 53	343 ± 29	184	2.6*
Dopamine				
Hypothalmus	361 ± 152	339 ± 87	94	0.12
Cortex	143 ± 97	163 ± 58	114	0.17
Striatum	4310 ± 540	4639 ± 496	107	0.65
Brainstem	40 ± 15	58 ± 18	145	0.76

*Significant at 5% level.
†Significant at 1% level.
‡Significant at 0.1% level.

Biochemical Assay

The biochemical assay data for the DB animals and their controls are presented in Table 1 and for the NPT in Table 2. These assays confirmed that the DB and the NPT animals had suffered extensive loss of NA from the cortex and hippocampus, with no alteration in brain DA. The DB animals also showed some loss of hypothalamic NA but the NPT animals were spared this damage.

Discussion

Since no differences in locomotor activity were detected in any of the activity tests used the simplest explanation of the dorsal bundle extinction effect, that of hyperactivity, can be convincingly ruled out.

The internal inhibition hypothesis of the dorsal bundle extinction effect predicted that the lesioned animals would be impaired in the suppression or withholding of a response, and so would be expected to have difficulty in acquiring the DRL which requires the inhibition of responding. This prediction was directly tested in the current experiment for both the DB and the NPT NA depleted preparations and neither showed any difficulty in learning to inhibit responding in order successfully to acquire a DRL response pattern. It is not possible to argue that the negative findings on this task were due to inadequate NA lesions, since not only do the biochemical data show extensive depletions but the selfsame animals that failed to differ from controls in the acquisition of the DRL schedule showed a marked resistance to extinction in a motor manipulative task [27]. Thus, there are situations in which DB and NPT animals show unimpaired response inhibition and so a general failure of internal inhibition cannot explain the resistance to extinction seen in these animals. Another, logically distinct, mechanism of perseveration is tested in the following experiment.

EXPERIMENT 2

In order to establish a prepotent response tendency DB animals were lever shaped (as described in Experiment 1) and then placed on a prolonged period of CRF training before being placed on the DRL schedule. This means that a tendency towards the emission of high rates of responding exists prior to transfer to another schedule, DRL, which requires suppression of responding for the DRL interval.

CRF pretraining, rather than a higher order schedule, was chosen since it is known that DB and NPT animals differ markedly from controls in the response rates emitted on at least some higher order schedules. It has been shown [34] that NPT animals respond considerably more rapidly on a FR 30 than controls, and this has been confirmed for DB animals as well [36]. DB animals also respond differently to controls on VI schedules [36]. Thus, the use of higher order schedules to generate high response rates prior to transfer to DRL almost certainly would have produced baseline differences which would have rendered the subsequent transfer uninterpretable. Neither DB nor NPT animals differ from controls on a CRF schedule [26,43]. Further, this CRF pretraining has been shown [6,38] to be effective in producing a deficit in subsequent DRL acquisition in hippocampally lesioned rats.

Behavioural Method

DB animals were prepared as previously described (DB control n = 10, treated n = 10). They were reduced to 90% of their free-feeding weight and maintained, as before, on 15 g of food per rat after each day's operant testing session. After lever shaping in the Skinner boxes as described in Experiment 1, they were trained on a CRF schedule for the following 15 days, each daily session lasting 25 min and only on Day 16 were they placed on the DRL schedule described in Experiment 1. There was no cue available to the animal to indicate that the schedule had changed from CRF to DRL. DRL acquisition then continued for the next 25 days.

Results

The acquisition of CRF occurred with equal rapidity for

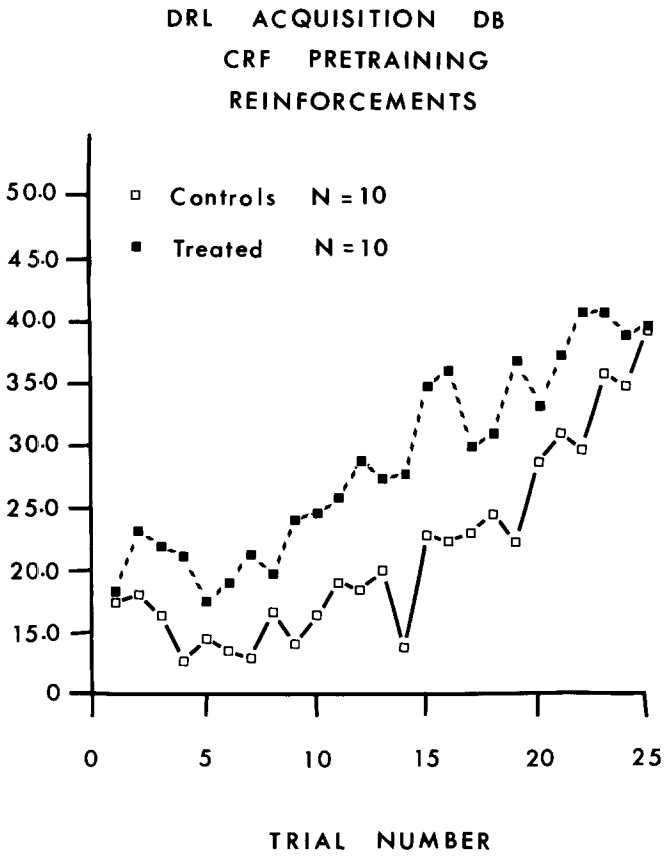

FIG. 2. Mean number of reinforcements per session obtained by DB animals during the 25 sessions of DRL acquisition which followed 15 days training on CRF.

both treated and control animals in the group. This confirms the lack of any impairment on CRF acquisition reported by previous authors for this preparation [26,43]. A two factor analysis of variance with repeated measures on one factor, days, showed no significant difference between the lesioned and control animals.

(DB between groups $F(1,18) = 0.53$, NS.)

When transferred to the DRL schedule the DB rats differed from their vehicle controls in showing more rapid acquisition of this schedule. The three measures recorded, number of lever presses, number of reinforcements and percent reinforced response all tended to show better acquisition by the DB lesioned rats, although some individual measures fell short of significance at the 5% level. Over the first half of the DRL acquisition following CRF pretraining the DB rats emitted fewer lever responses, obtained more rewards and showed a higher percent reinforced responses measure than their controls. This effect was particularly noticeable in the number of reinforcements obtained by the DB animals which demonstrated a higher reward rate than their controls for almost all the 25 days of acquisition (Fig. 2). A two factor analysis of variance with repeated measures on one factor days was carried out on the data.

Lever responses:
DB, interaction $F(24,342) = 1.55$, $p<0.05$
Reinforcements:
DB, between groups $F(1,18) = 5.44$, $p<0.05$
Percent reinforced responses:
DB, between groups $F(1,18) = 2.96$, $p<0.10$, NS.

Biochemical Results

The results of the biochemical assay of brain catecholamines are presented in Table 3 for the DB animals and their vehicle controls. Again, severe depletions of cortical and hippocampal NA were achieved with no alteration of brain DA.

Discussion

The DB rats showed no impairment in the acquisition of the DRL schedule despite heavy pretraining on CRF prior to transfer to DRL. This is clearly contrary to the perseverative hypothesis of the resistance to extinction seen after dorsal bundle lesions. In fact a strong hint of improved acquisition emerged for the DB group following CRF pretraining. Despite considerable training on the high

TABLE 3

DORSAL BUNDLE: REGIONAL CONCENTRATIONS OF AMINES; VALUES ARE MEANS IN NANOGRAMS PER GRAM TISSUE WITH STANDARD ERROR OF THE MEAN

	Control (n=10)	Treated (n=10)	%	*t* statistic
Noradrenaline				
Hippocampus	256 ± 50	28 ± 21	11	4.2‡
Hypothalamus	752 ± 91	306 ± 96	40.6	3.3†
Cortex	265 ± 49	37 ± 6	14.2	4.6‡
Cerebellum	207 ± 18	197 ± 25	95.3	0.32
Dopamine				
Hypothalamus	164 ± 114	195 ± 83	118	0.22
Cortex	146 ± 30	116 ± 28	79.5	0.73
Striatum	5364 ± 597	7246 ± 1005	135	1.61

*Significant at 5% level.
†Significant at 1% level.
‡Significant at 0.1% level.

rates of responding engendered by CRF pretraining the DB group did not perseverate in this high response rate when transferred to the DRL schedule. In fact this CRF pretraining, rather than impairing subsequent DRL acquisition, as would be predicted by the perseverative hypothesis, actually appeared to help the lesioned rats achieve a DRL response pattern. That this beneficial effect in Experiment 2 is due to the CRF pretraining and is not intrinsic to the DRL schedule is shown by the lack of superiority of the lesioned rats in Experiment 1 in which no pretraining was given. Thus, the perseverative hypothesis of the dorsal bundle extinction effect must be rejected on the basis of the present data.

GENERAL DISCUSSION

The first point to emerge from the preceding experiments is that, contrary to the prediction of the coeruleo-cortical model [9, 10, 11, 17] of learning, near total destruction of the dorsal noradrenergic bundle, using two distinct techniques, the DB and the NPT preparations, did not impair acquisition learning in any general way. The DRL acquisition of both the DB and the NPT rats in Experiment 1 did not differ from controls, nor did the CRF acquisition in Experiment 2. In fact, destruction of the dorsal noradrenergic bundle seemed to enhance learning of a DRL task if this had been preceded by CRF pretraining in Experiment 3. Thus, this adds to previous evidence [1, 16, 25, 26, 27, 28, 29, 31, 37, 39] excluding the locus coeruleus and the dorsal noradrenergic bundle from any role as a general mediator of reinforcement in the learning process.

Secondly, several hypotheses suggested to explain the resistance to extinction seen after dorsal bundle and NPT lesions have been tested and found wanting. General hyperactivity was tested in Experiment 1, internal inhibition in Experiment 1 and perseveration in Experiment 2. None of these adequately explained the available data.

Other theories of the dorsal bundle extinction effect have been suggested elsewhere. Deficits in the memory of non-reward have been found in certain situations [28], and this could clearly affect extinction behaviour. It might also give rise to the improved DRL acquisition after CRF pretraining, since Dickinson [13] has suggested that the response invigorating effects of nonreward [2] predominate during the transfer from CRF to DRL and these act to impair the performance of normal animals by giving rise to a high response rate which is incompatible with DRL performance. Failure to remember previous nonreward would thus actually help acquisition of this task in the lesioned rats. Another suggested effect of dorsal bundle lesion is to make the animals more distractible [37] and this assumption of increased stimulus sampling can also give rise to resistance to extinction [22,41]. On this model the CRF to DRL transfer can be regarded as a nonreversal shift which has been shown to benefit from increased stimulus sampling [23,24]. This attentional model of the dorsal bundle function has been tested elsewhere [29,31].

Whatever the explanation of the improved DRL acquisition in the lesioned rats, the failure to increase response rates as much as controls after a reduction in reward density (which here actually helped the lesioned rats) has been seen in other situations as well. Dorsal bundle lesioned rats respond less than controls when transferred from a CRF to a VI (variable interval) schedule [36] and also when the density of reward is reduced on a two-lever VR (variable ratio) schedule [31]. This contrasts markedly with the increased responding relative to controls when reward is withdrawn completely, as in extinction [4, 25, 26, 27, 28, 32, 43, 44]. Any theory of dorsal bundle function must be able to incorporate this difference within its framework [30].

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