# Sensitization to apomorphine in pigeons: a multifactorial conditioning process

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**Apomorphine (apo), an unspecific direct dopamine agonist, elicits an intense and lasting pecking bout in pigeons. Apo yielded orderly dose–response functions, and repeated administrations led to sensitization. Strain and individual differences in sensitivity to apo were at least partly due to genetic factors. However, a strong cage-context dependency of the sensitization, which is indicative of conditioning, occurred in both pigeon strains studied. Apo-induced pecking and sensitization also occurred in total darkness. Pigeons could be conditioned to discriminate between an apo state and a non-apo state. A small dose of apo was effective as a conditioned stimulus when paired with a high dose as an unconditioned stimulus. The conditioned response (CR) was strongly specific to the context in which the sensitization to apo took place. The resistance to extinction of the CR could be increased through an oversensitization treatment. The incremental responses arising during the sensitization treatment and the CRs shown afterward by individual pigeons correlated significantly. The sensitization to apo in pigeons is well accounted for by a conditioning schema in which an interoceptive drug state is a conditional conditioned stimulus for the full expression of the incremental response. Variants of the scheme might also account for the sensitization of rodents to psychostimulants. A neural model that embodies the characteristics of the conditioning scheme has been proposed. *Behavioural Pharmacology* 26:139–158**

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## Introduction

The repeated administration of many drugs leads to the development of tolerance – that is, to a progressive diminution of their physiological or behavioral response-eliciting efficacy (Kalant, 1989). This adaptive process can be viewed as being part and parcel of a general disposition of organisms to maintain a relative constancy of their *milieu interieur* (Poulos and Cappell, 1991; Gollwitzer *et al.*, 2000). The widespread occurrence of habituation, that is, the reduction of neural or behavioral responses to repeatedly presented exteroceptive stimuli, is an analogous phenomenon (Groves and Thompson, 1970; Domjan, 1997). This categorization should not be understood as implying that the proximal, physiological processes underlying specific instances of tolerance, or indeed habituation, are straightforward; whenever investigated in detail, the mechanisms of both tolerance and habituation have turned out to be intricate (cf. Staddon and Higa, 1996; Peper, 2004; Siegel, 2005; Leussis and Bolivar, 2006).

The fact that the repeated administration of a smaller number of drugs leads to an increase in their efficacy is counterintuitive from the above homeostatic point of view. This pharmacological sensitization and the analogous behavioral sensitization that occurs with certain exteroceptive stimuli (Domjan, 1997) are less easy to account for than drug tolerance and stimulus habituation. Because a sensitizing capacity has been thought to be a characteristic of psychostimulants with addictive potentialities (Stewart and Badiani, 1993; Morgan *et al.*, 2006; but see Ahmed and Cador, 2006), the sensitization phenomenon has received much research attention. This is despite the fact that actual addiction to psychostimulants has often been related to the development of tolerance to them (Leith and Kuczenski, 1981; Hammer *et al.*, 1997; Mendelson *et al.*, 1998), an issue to which we return in the Discussion section. The emergence of sensitization has been variously attributed to a change in drug excretion, to modifications in drug metabolism, to an accumulation of drug metabolites, to an increase in the number of drug-relevant molecular receptors, to behavioral sensitization, or even habituation to the experimental contexts, to an associative conditioning of the drug response to that context, or to various combinations of these processes (cf. Stewart and Vezina, 1991; Willner *et al.*, 1992; Stewart and Badiani, 1993; Hooks *et al.*, 1994; Mattingly *et al.*, 1997; Tirelli and Heidbreder, 1999; Zavala *et al.*, 2000; Crombag *et al.*, 2001; Anagnostaras *et al.*, 2002; Tirelli *et al.*, 2005; Uslaner *et al.*, 2006; Carey *et al.*, 2008; Carrera *et al.*, 2011).

Apomorphine (apo) is a highly potent direct dopamine agonist that activates both D1-type and D2-type dopamine receptors. Its behavioral effects are of wider interest because the dopaminergic transmission system is

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generally considered to play an important role in the development of abusive consumption of a variety of drugs (Heidbreder *et al.*, 2005). Indeed, apo has some pharmacobehavioral characteristics in common with the psychostimulants cocaine and amphetamine, both indirect and unspecific agonists of dopamine. However, the repeated intake of apo as a treatment strategy for Parkinson's disease and for sexual dysfunction only rarely leads to a psychological or physiological dependency in humans (Lowinson *et al.*, 1997; Téllez *et al.*, 2006). Most of the research on sensitization has focused on the locomotor hyperactivity that rats and mice exhibit in response to cocaine and amphetamine, as well as in response to apo. Less attention has been paid to more specific stereotypic behaviors such as gnawing and grooming that are also elicited by these drugs.

We have studied the sensitization increment of an easy-to-quantify behavioral stereotypy induced by apo in birds. Pecking elicited by apo in birds is an impressive response. A medium dose, for example, 0.5 mg/kg, systemically administered to a pigeon – with the exception of some rarely found unresponsive birds – yields a bout of activity consisting of some $2000_{\pm}$ pecks and lasting about 1 h. The pecks are usually directed at small contrasting inedible stimuli present on the walls or, less frequently, on the floor of their cages, or on the pigeon's own body. They may also be directed at food morsels, but these are usually dropped and not swallowed. In earlier publications, we have explored several of the variables influencing this spectacular response (Deviche, 1983; Delius, 1985; Lindenblatt and Delius, 1987, 1988; Burg *et al.*, 1989; Siemann and Delius, 1992a; Wynne and Delius, 1995, 1996; Godoy and Delius, 1999; Keller and Delius, 2001; Keller *et al.*, 2002; Acerbo *et al.*, 2003a, 2003b; Acerbo and Delius, 2004).

The present paper reports a series of experiments that further clarify the pecking-inducing effect that apo has on pigeons and the ensuing sensitization process. We examine whether the sensitization that occurs with respect to pecking can be accounted for by Pavlovian learning using differentiation (discrimination) procedures that control for pseudoconditioning (Domjan, 1997). The conditioning scheme we propose departs from the fact that injected apo acts as an unconditioned stimulus (US) that elicits an unconditioned pecking response (UR). Furthermore, repeated injections in a given cage environment lead to a sensitized pecking response (SR). The response increment (IR = SR–UR) is assumed to be a conditioned pecking response (CR) elicited by the conditioning stimulus (CS) cage context ($CS_{cage}$) and the interoceptive conditioning stimulus apo ($CS_{apo}$) coacting in a multiplicative conditional way ($CS_{apo} \times CS_{cage}$) that effectively yields $CR_{apo \times cage}$. We then briefly discuss whether the sensitization and addiction to psychostimulants occurring in rodents and humans can be accommodated through variants of the proposed learning model. We also sketch a neural model that functions in a manner that agrees with the conditioning scheme. Finally, we consider whether the pigeon/apo preparation could serve as a model for the study of addiction. We begin, however, by reporting an experiment that establishes the dose dependency and time course of the apo sensitization. Two experiments show that the apo responsiveness of pigeons is affected by genetic factors, much as it has been shown to be the case in rats (Cools, 1994). Finally we report six experiments that examine a number of corollary derivations pertinent to the conditioning hypothesis.

## Methods

### Subjects and drugs

The pigeons (*Columba livia*) used were all adults of homing stock, weighing between 450 and 550 g. They originated either from a local Bochum, northwest Germany, breeder (74 pigeons), or from a local Konstanz, southwest Germany, breeder (116 pigeons). The birds were routinely housed in a large outdoor aviary and brought in as needed for the various experiments at least 1 week before they began. While taking part in the experiments, they were individually housed in stainless steel grid cages ($45 \times 45 \times 48$ cm) located in a well-ventilated, brightly lit room with a 12 : 12 h light : dark cycle. The pigeons were all pharmacologically naive before the experiments began. The treatments involved pectoral muscle injections of 0.1–1 mg/kg aqueous racemic apo-hydrochloride solution (10 mg/ml apo; Teclapharm, Lüneburg, Germany) – depending on the particular experiment (see below) – diluted to a ratio of 1 : 5 with deoxygenated saline, or injection of control saline solution (sal). All treatments described in this paper complied with the German animal welfare laws and regulations.

### Procedures

#### *Experiment 1: dose–response functions*

The first experiment addressed the dose dependency of apo sensitization. Bochum stock pigeons were randomly assigned to six groups and were injected each day for six consecutive days with either 0.0 mg/kg ($n = 7$), 0.1 mg/kg ($n = 6$), 0.2 mg/kg ($n = 8$), 0.3 mg/kg ($n = 6$), 0.5 mg/kg ($n = 16$ birds), or 1.0 mg/kg ($n = 7$) doses of apo. The pigeons were then individually placed into experimental cages located in a separate, brightly lit room and video-recorded while in the experimental cages for 20 min before being returned to their home cages. The experimental cages used (Fig. 5, cubic cage) were modified standard cages with their inner back-wall and side-wall surfaces lined with white panels speckled with dark green dots (pecking targets: 0.8 cm in diameter, about $10/100\,cm^2$). Four of these test cages were located in a separate, brightly lit room equipped with a video-camera and video-recorder. The videotapes were reviewed afterward and the pecks issued by the pigeons were

counted with the help of a computer that was programmed to function as a tally counter. The apo-induced pecks of pigeons are quite distinct, easily recognizable motions (Siemann and Delius, 1992a, 1992b; Hörster *et al.*, 2002) permitting accurate counts that reliably yield interobserver concordance coefficients ($r_s$) of 0.85 or higher. With four pigeons of the 0.5 mg/kg group, the procedure was slightly different: the duration of testing for these pigeons was extended to 95 min on days 1, 2, and 5, and their pecks were counted over each of 19 consecutive 5-min periods.

***Experiment 2: stock differences***

The second experiment sought to establish whether Konstanz and Bochum stock pigeons differed in their courses of apo sensitization when tested under strictly comparable conditions. Two groups of eight birds each were included in the experiment. Four pigeons at a time, two Bochum and two Konstanz pigeons, were injected with 0.5 mg/kg apo and immediately placed into the test cages and videotaped for 20 min before being returned to their home cages. Each of the 16 pigeons was treated thus for six consecutive days.

***Experiment 3: selected parentage***

The next experiment explored the bases of individual differences in apo sensitivity using pigeons bred from Konstanz stock parent birds earlier identified as either high or low apo responders. Two breeding pairs were assembled with pigeons that had proven to be virtually apo-unresponsive in a previous experiment. Two other pairs were assembled in which one partner had been shown to be apo-unresponsive and the other partner had been shown to be highly apo-responsive. Two further pairs were assembled with partners that had both proven to be highly responsive in preceding apo-sensitization experiments. They were housed in large breeding cages provided with a nesting bowl. The cages were placed in a quiet, well-ventilated room that was lit on a 16 h-on–8 h-off cycle. Their offspring were fitted with numbered leg rings, separated from their parents when they were about 2 months old, and placed in an outside aviary until they were fully grown about 4 months later. From the offspring produced by the six breeding pairs over a period of about 1.5 years, we formed three groups of, respectively, 15, 15, and 14 pigeons. These pigeons were apo-tested in the experimental cages for 20 min for 6 days. Five of the unresponsive-parentage pigeons and eight of the responsive-parentage pigeons were further injected with saline instead of apo before being placed into the experimental cage on days 7–9.

***Experiment 4: sensitization context specificity***

This experiment examined whether the sensitization to apo of Bochum stock pigeons would be as context-dependent and as resistant to latent inhibition as has been found to be the case in Konstanz stock pigeons (Godoy and Delius, 1999; Acerbo *et al.*, 2003b). Pigeons of Bochum stock were assigned to two groups of eight pigeons each. In phase I, the pigeons of one group were injected with 0.5 mg/kg apo and exposed to black-walled, yellow-triangled (0.10-cm sides, about 10/100 $cm^2$) cylindrical cages (Fig. 5, cages) on six consecutive mornings (I Apo cyl treatment). In the afternoons, the same pigeons were injected with saline and exposed to the usual white-walled, green-dotted cubic cages (I Sal cub treatment). In phase II, these same pigeons were injected on six further mornings with 0.5 mg/kg apo and exposed to the white-walled, green-dotted cubic cages (II Apo cub treatment). The pigeons of the second group were only exposed to cubic cages under apo for 20 min for six consecutive days (I Apo cub treatment).

***Experiment 5: sensitization in darkness***

Experiment 5 examined whether degradation of the visual context cues through a darkened condition, as compared with a lit condition, would have a depressing effect on the sensitization to apo. The experimental cage used was an enclosure (40 × 20 × 20 cm) made of transparent plastic. Its walls were externally lined with white cardboard speckled with dark green dots (8 mm diameter, about 10 dots/100 $cm^2$). The floor was covered with white absorbent paper. The cage was located within a force-ventilated, thick-walled, wooden, sound-damping chamber (80 × 40 × 50 cm). A microphone and a wide-angle infrared/visible light-sensitive video-camera were placed within the chamber and above the cage. The chamber was either invisibly illuminated with infrared power diodes (950 nm), kept totally dark, or lit with a white fluorescent tube yielding an ~100 lx luminance within the cage. The microphone was connected serially to a variable gain amplifier, an adjustable bandpass filter, an adjustable pulse former, and an electronic counter (Neurolog, Welwyn Garden City, England). The system was tuned to selectively register the sound pressure peaks produced by pecks; the extent to which this was achieved has been reported under the Results section.

Pigeons of Konstanz stock were randomly assigned to two groups of six birds each. There were two successive experimental phases, the first lasting 7 days and the second lasting 6 days. Alternate pigeons of each group were injected with 0.5 mg/kg apo in the mornings and with saline in the afternoons, and vice versa. In both cases the pigeons were exposed to the experimental cage while the microphone counting system was active. During the first phase the light/dark group pigeons were exposed to the lit cage after apo and to the dark cage after saline. During the second phase they were treated in the reverse manner. The dark/light group pigeons were treated the other way round. Three pigeons of each group were also videotaped under the dark condition, this being done under the aforementioned infrared illumination.

***Experiment 6: apomorphine–saline discrimination***

Experiment 6 examined whether apo would function as an interoceptive discriminative, drug-state stimulus for pigeons, using a drug-conditioning procedure. Six pigeons of Konstanz stock were kept food deprived to 80% of their normal weight for the duration of the experiment. Horizontal conditioning platforms controlled by a personal computer (Xia *et al.*, 1995) were attached to the pigeons' home cages, replacing their feeding troughs. Each platform bore two side-by-side transparent pecking keys (centers 5 cm apart, diameter 2.5 cm). Two light-emitting-diode matrices (5 × 7 diodes, 12 × 17 mm) served to present diamond-shaped stimuli formed by five lit diodes. These diodes were green-lit under the right key and red-lit under the left key. Separate solenoid feeders could deliver rewards consisting of a few grains of millet on either key.

The pigeons were allocated into two groups of three pigeons each. For one group the green right key was deemed correct when the pigeons were previously injected with apo, and the red left key was deemed correct when they were previously injected with saline; for the other group, it was the other way round. The pigeons were first trained to peck the keys in daily sessions lasting 150 trials each. Throughout the experiment the pigeons were injected in a quasi-random order (Gellermann, 1933) with either 0.25 mg/kg apo or saline, 10 min before the start of a session. The apo dose used was selected on the basis of preliminary findings from a different set of pigeons; higher apo doses interfered by eliciting key-unrelated pecking, whereas lower doses seemed insufficient to produce a detectable drug state. During the key-pecking training phase, each trial began with a 20-s pause during which the stimuli were off and the keys were deactivated. When the pause was over, only the drug state-correct key was stimulus-lit and activated for a period lasting at the most 8 s. The drug state-incorrect key remained dark and inactivated. A peck delivered to the correct key extinguished the stimulus and delivered a reward onto the same key. The pause initiating the next trial followed. However, if the pigeon did not peck during the 8-s illuminated-key period, a reward was automatically issued on the relevant key before the pause began (autoshaping, Brown and Jenkins, 1968). As soon as 75% of the trials of a session yielded key pecks, the pigeons entered the discrimination training phase.

During the discrimination training phase the pigeons were subjected to six after-apo and five after-saline quasi-randomly sequenced once-daily discrimination training sessions. These sessions lasted about 50 min, consisting of 350 trials each. Each trial began with a 5-s pause, during which the keys were dark and inactive. Next, the two discriminative stimuli were displayed under the keys until the pigeon pecked one of the keys twice. When the pecks were directed at the key showing the correct stimulus they yielded a grain reward followed by a 2-s feeding period with the stimuli still lit. Two pecks to the key displaying the incorrect stimulus yielded a penalty consisting of a 2-s time-out with the whole diode matrix lit. From the third session onward, three pecks on one or the other key were required before a reward or a penalty was issued; from the seventh session onward, six such pecks were necessary.

The test phase that followed comprised 14 daily sessions in which the pigeons were randomly tested under the influence of either apo or saline. Six of these 14 sessions were intercalated retraining sessions exactly as described above. The eight proper test sessions consisted of 100 trials each. Half of these sessions took place after apo injections and half after saline injections. All trials were preceded by a 20-s pause, followed by the presentation of both stimuli, and were terminated by a single peck. The pecks pertaining to the first six feedback-free trials of each test session were counted separately according to which key was pecked but were neither rewarded nor penalized, leading instead directly to the pause initiating the next trial. Furthermore, during this initial phase of the test sessions, the subjects were watched from behind a screen provided with a peephole. In all 94 remaining trials the pigeons were rewarded or penalized after single-key pecks but otherwise the trials were conducted according to the procedure described in the previous paragraph.

***Experiment 7: apomorphine autoconditioning***

This experiment examined whether a low dose of apo would act as a CS after having been repeatedly paired with a high dose of apo that served as an US. During a first, sensitization phase, all 18 participating pigeons of Konstanz stock were treated with apo to ensure a sensitized, stable, near-asymptotic pecking response to the drug. For this they received a daily 0.9 mg/kg apo dose over six consecutive days. The dose was chosen to yield a strong pecking UR without risking beak injuries (see Experiment 1, the Results section). After each injection they were placed in the cylindrical green-dotted experimental cages for 20 min. Two pigeons that were notably unresponsive to this relatively high dose of apo were excluded. Before the second 5-day conditioning phase began, the remaining 16 pigeons were allotted to two groups of eight pigeons approximately matched according to the pecking they had yielded at the end of the sensitization phase. Each day all the birds were injected with 0.1 mg/kg apo ($CS_{apo}$) and placed in the same cylindrical experimental cages for 10 min. The pigeons of the contingent group were then briefly taken out of the experimental cage, injected with a 0.9 mg/kg dose of apo (US), and placed back into the experimental cage for a further 20 min. This complied with a so-called delayed conditioning procedure (Domjan, 1997). The pigeons of the noncontingent group were also taken out of the

experimental cage after 10 min but were returned to their home cages; about 2.5 h later, they were injected with a 0.9 mg/kg dose of apo and again placed in the experimental cages for 20 min. During a subsequent testing phase lasting 3 days, the pigeons of both groups were injected daily with the 0.1 mg/kg apo dose and placed in the experimental cages for 30 min.

### *Experiment 8: conditioned response context specificity*

This experiment sought to confirm that the CR to an experimental cage was similarly context specific as the sensitized response had been found to be. Konstanz stock pigeons were randomly assigned to two groups of six birds each. The pigeons of one group were injected daily every morning with 0.5 mg/kg apo and individually placed into black-walled, yellow-triangled cylindrical experimental cages for six consecutive days. In the afternoon, the same pigeons were injected with saline and individually placed into green-dotted white-walled cubic experimental cages. The pigeons of the other group were treated in the same way but with the two types of experimental cages reversed. During a second phase, all the pigeons were injected with saline in the morning and afternoon for four consecutive days and then placed either into the black-walled yellow-triangled cylindrical cage or into the white-walled green-dotted cubic cage according to the same allocations as before.

### *Experiment 9: oversensitization and conditioned response*

The final experiment explored whether, in analogy to overtraining in conventional conditioning preparations, the apo-induced CR would evince an increased resistance to extinction following an oversensitization treatment. Pigeons of Konstanz stock were assigned to two groups. The oversensitized group ($n=9$) received 16 once-daily 0.5 mg/kg apo injections starting on day 1. The norm-sensitized group ($n=9$) received six once-daily 0.5 mg/kg apo injections starting on day 11. After being apo-injected, all pigeons were placed in experimental cages for 20 min, and they were video-recorded there on days 1, 11, and 16. On days 17–20 the pigeons of both groups received saline injections before being placed in the experimental cages and were video-recorded again for 20 min.

### Statistical analyses

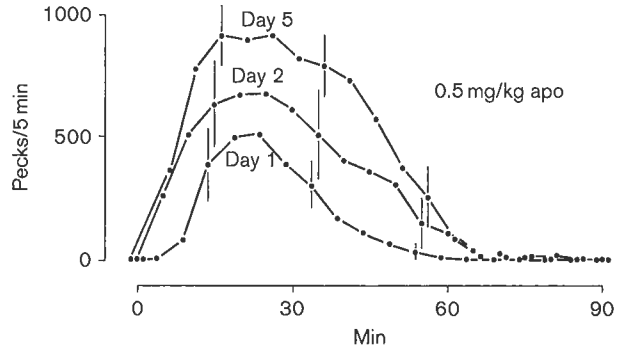
The mean daily peck counts and standard errors (SEs) were calculated for each of the experimental groups. Because of a frequent and pronounced non-normality of the data sets obtained, nonparametric Wilcoxon $T$, Mann–Whitney $U$, Jonckheere $Z$, and Spearman $r_s$ statistics were used to assess the one-tailed significance of within-group and between-group response differences; $P$-values of up to 0.05 were taken to indicate significance.

## Results

### Experiment 1: dose–response functions

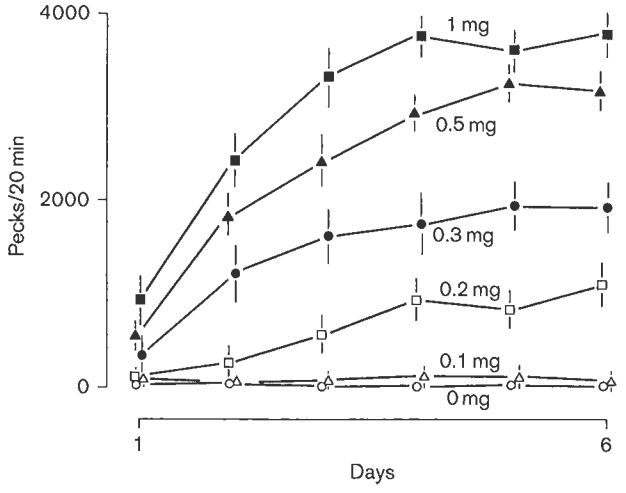
The mean ± SE pecking scores per successive 5 min, over the duration of the three extended sessions on days 1, 2, and 5, of four pigeons belonging to the 0.5 mg/kg dose group are shown in Fig. 1. Note that in accordance with the sensitization effect, to be detailed below, the overall pecking response increased across the three sessions. Note too that on all 3 days, pecking began 5 min after the injection at 0 min and that a peak pecking rate was reached at the latest by the 20–25-min period after the apo injection. The pecking rate fell to baseline levels

**Fig. 1**




Experiment 1, response courses. Mean pecks per 5-min period over 90-min sessions on Days 1, 2, and 5 of four pigeons receiving 0.5 mg/kg doses of apo at the beginning of each session. The means ± SE values were computed for the 0th, 3rd, 7th, 11th, and 15th 5-min periods. For the 0th and 15th periods the ± SE ranges fell within the data point diameters. Apo, apomorphine.

**Fig. 2**




Experiment 1, dose dependency of the sensitization to apomorphine. The mean ± SE pecks over six successive daily 20-min sessions, each preceded by an apo injection of between 0 and 1 mg/kg apo. Group sizes were as follows: 0.0 mg, $n=7$; 0.1 mg, $n=6$; 0.2 mg, $n=8$; 0.3 mg, $n=6$; 0.5 mg, $n=16$; 1.0 mg, $n=6$.

between the 60 and 65 min or the 70 and 75 min periods after apo administration. Within the 15–20, 20–25, 30–35, 40–45, and 55–60 min periods all four pigeons showed an increase in pecking from day 1 to day 2 and again from day 2 to day 5. Within all other periods, one or more pigeons broke at least once with this maximal pattern.

The session mean ± SE values pertaining to the different apo dose groups are shown in Fig. 2, plotted as a function of the successive daily sessions. (One of the 1 mg/kg apo group pigeons had to be removed from the experiment because it developed a beak injury as a result of its extremely intense pecking.) It is evident that the pecking responses increased up to dose-dependent near-asymptotes when doses of more than 0.1 mg/kg apo were repeatedly administered (day 6, $Z = 3.03$, $P < 0.001$).

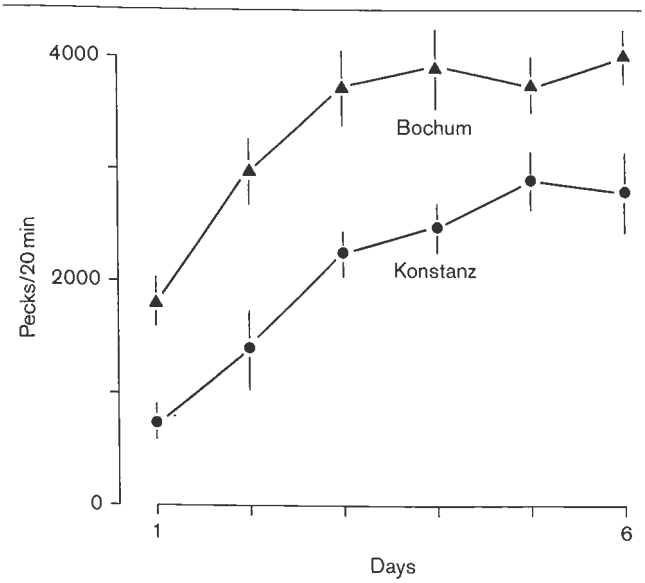
### Experiment 2: stock differences

Figure 3 shows the courses of apo sensitization, over 6 days of apo treatment, of the two groups of eight pigeons each. The Konstanz pigeons yielded a mean of 721 ± 202 pecks on day 1 and a mean of 2668 ± 337 pecks on day 6, having reached a close-to-asymptotic level on day 5. The Bochum pigeons yielded a mean of 1878 ± 273 pecks on day 1 and a mean of 3910 ± 255 pecks on day 6, having reached a near-asymptotic level on day 3. The differences between the groups were significant at least at $P$-values of less than 0.05 [all $U$s(8,8) ≤ 14] on each of the six treatment days. Nevertheless, the two least apo-responsive pigeons of the Bochum group showed courses of sensitization that were similar to those of the two most apo-responsive pigeons of the Konstanz group (not shown). The response increase from day 1 to day 6 was significant at $P$-values of less than 0.01 in both groups [both $T$s(8) ≥ 35].

### Experiment 3: selected parentage

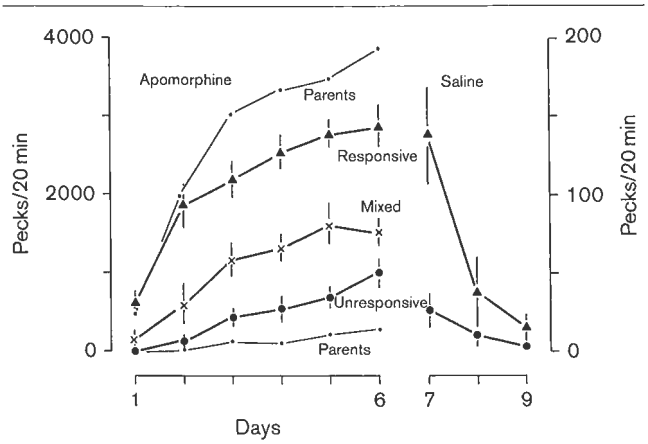
The mean pecking scores of the pigeons of apo-unresponsive, apo-mixed, and apo-responsive parentage during apo treatment days 1–6 are separately shown in Fig. 4. For completeness we also show the mean sensitization curves of the apo-unresponsive and apo-responsive parent birds. The differences on days 1–6 between the responsive-parentage, mixed-parentage, and unresponsive-parentage groups were all significant at least at $P$-values of less than 0.05 [all $U$s(15,14) ≤ 57, all $U$s(15,15) ≤ 63], except for the differences between the apo-unresponsive and mixed responsive–unresponsive groups on days 1 and 2 [both $U$s(15,15) ≥ 80]. The increases in response between day 1 and day 6 were significant at $P$-values of less than 0.05 [$T(15) = 92$] for the unresponsive-parentage birds and at $P$-values less than 0.01 for the mixed-parentage birds [$T(15) = 103$] and the responsive-parentage birds [$T(14) = 110$]. Despite these differences between means, there was some overlap between the individual pecking scores of the three groups of pigeons. Figure 4 also shows the mean pecking scores under saline (extinction) treatments (days 7–9) for the subsamples of pigeons with apo-responsive parents and apo-unresponsive parents. The difference between the responsive-parentage and unresponsive-parentage group CRs was significant on day 7 [145 ± 26 against 26 ± 7 pecks, $P = 0.05$, $U(5,7) = 6$] but not on days 8 and 9 [$U$s(5,7) ≥ 12].

**Fig. 3**




Experiment 2, stock differences. The mean ± SE pecking scores upon daily repeated administration of 0.5 mg/kg doses of apo (days 1 to 6) to pigeons of Konstanz stock ($n = 8$, ●) and Bochum stock ($n = 8$, ▲).

**Fig. 4**

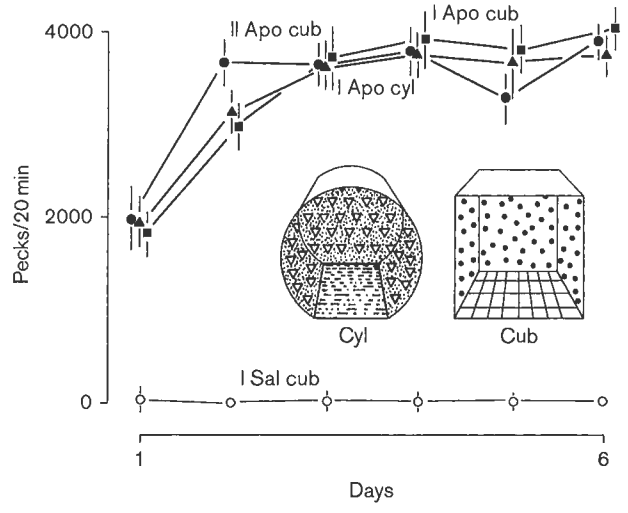



Experiment 3, selected parentage. The mean ± SE pecking scores during apo sensitization (days 1 to 6) of pigeons of apo-responsive parentage ($n = 14$, ▲), mixed responsive–unresponsive parentage ($n = 15$, ×), and unresponsive parentage ($n = 15$, ●). The mean sensitization curves of the apo-responsive or apo-unresponsive parent pigeons are shown by thin lines. Also shown are the mean ± SE curves under saline treatment (days 7 to 9) of pigeons with apo-responsive parents ($n = 7$, ▲) and apo-unresponsive parents ($n = 5$, ●).

### Experiment 4: sensitization context specificity

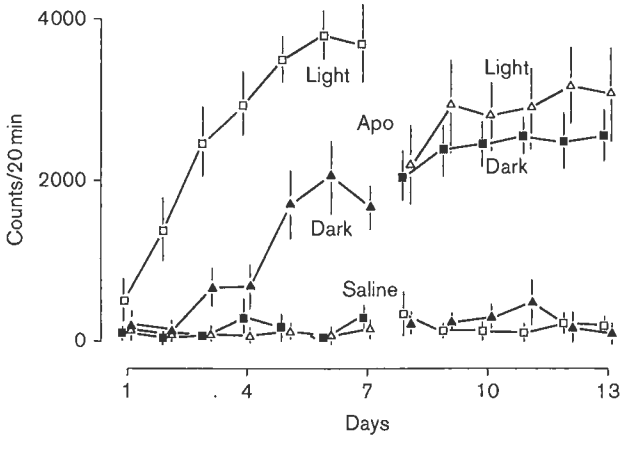
The results of this experiment are presented in Fig. 5. The pigeons first treated with apo in the cylindrical cages (I Apo cyl) and with sal in the cubic cages (I Sal cub) showed a sensitization course in the cubic cages that was not significantly different from that shown in the same cage by pigeons that had not been saline pretreated [II Apo cub and I Apo cub, day 1 to day 6 response increments: $1931 \pm 232$ against $2010 \pm 173$ pecks/20 min, $U(8,8) = 26$]. Comparison of these two groups' initial responses in the cubic cages revealed no evidence of any significant transfer of the sensitization acquired in the cylindrical cages to the cubic cages by the pretreated group [day 1 responses: $1990 \pm 497$ against $1942 \pm 214$, $U(8,8) = 31$].

Fig. 5




Experiment 4, context specificity of sensitization to apo in Bochum stock pigeons. The mean ± SE pecking scores are shown for the courses of sensitization of pigeons ($n = 8$) exposed in phase I to both cylindrical cages under apo (I Apo cyl, ▲) and cubic cages under saline (I Sal cub, ○) and then in phase II to the cubic cages under apo (II Apo cub, ●). The course of sensitization of pigeons ($n = 8$) only exposed to cubic cages under apo (I Apo cub, ■) is similarly shown. Insert: schematic cylindrical and cubic cages. Apo, apomorphine; cub, cubic; cyl, cylindrical.

Fig. 6




Experiment 5, apomorphine-induced pecking of pigeons in a light cage and in a dark cage: mean ± SE of acoustic peck counts. One group of pigeons ($n = 6$) was apo treated daily first in the light cage (□) and then in the dark cage (■). The other group ($n = 6$) was apo treated first in the dark cage (▲) and then in the light cage (△). The concurrent daily saline treatments always took place in the alternative lighting condition. Apo, apomorphine.

### Experiment 5: sensitization in darkness

The peck counts obtained with the microphone system exceeded those derived from the video-recordings by around 20%. The excess arose through wing and tail feathers making noisy contact with the cage walls when the pigeons walked about under the light condition or when they preened under the dark condition. The concordance between the two types of counting was nevertheless quite high ($r_s = 0.84$). The thus-validated acoustic count data of all 12 pigeons over all 13 days are summarized in Fig. 6. During the first phase, both groups (light/dark and dark/light) showed significant sensitization [light, day 1: $505 \pm 242$, day 7: $3988 \pm 337$; dark, day 1: $212 \pm 134$; day 7: $1680 \pm 272$, $P$s $< 0.05$, $T$s$(6) \geq 19$, respectively]; all 12 pigeons did in fact show a response increment. However, the near-asymptotic responding reached on day 7 by the light/dark group was significantly higher than that reached by the dark/light group on the same day [$P < 0.01$, $U(6,6) = 2$]. When the lighting conditions were reversed, the mean responding of the light/dark group fell by a marked amount [day 8: dark: $2018 \pm 223$, $P < 0.05$, $T(6) = 20$], whereas that of the dark/light group rose by a small amount [day 8: light: $2181 \pm 507$, $P < 0.05$, $T(6) = 19$]. When switched from the light to the dark condition all six pigeons showed a marked fall in responding; when switched from the dark condition to the light condition only four of the six pigeons showed a small rise in responding. The slight rises that occurred between days 8 and 14 were not significant for either group [both $T$s$(6) \leq 15$]. Furthermore, there was no significant difference between the groups on either of these 2 days [both $U$s$(6,6) \geq 13$]. The after-saline exposures yielded low pecking scores throughout the experiment without revealing any significant fluctuations.

### Experiment 6: apomorphine–saline discrimination

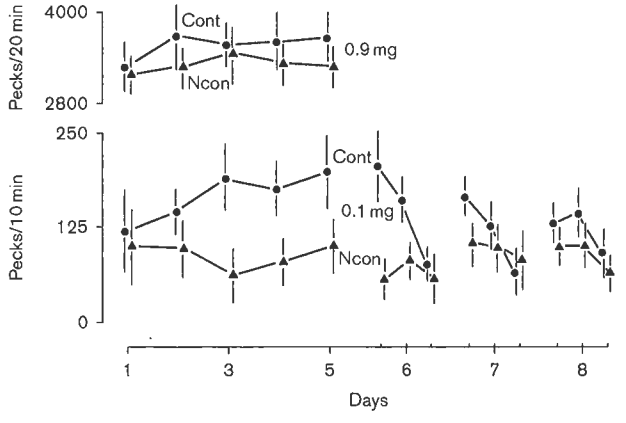
At the end of the discrimination training phase, the six birds produced an average of $96 \pm 2\%$ correct trials per session. In itself this provides no evidence of a discrimination between the apo state and the saline state, as at the beginning of each training session the pigeons could have hit the correct key by chance and kept to it. Alternatively, they could have quickly switched to the correct key after being penalized for pecking the

incorrect key and then simply persisted in responding to the correct key on the basis that it consistently yielded a reward. Thus, only the initial six nonreinforced trials of the test sessions provided a true feedback-free measure of a pigeon's drug-state discrimination performance. Across the six pigeons, the mean ± SE percentage of correct test choices under the apo state was 79 ± 9%; under the saline state it was 97 ± 5%. Pooled together over both states the correct choices amounted to a mean of 88 ± 6%. This mean discrimination score significantly exceeded the chance 50% choice level [$P < 0.05$, $T(6) = 20$]. Apo was thus a stimulus that pigeons could detect even at the relatively small 0.25 mg/kg dose. During at least the critical six initial trials of the eight test sessions, none of the six pigeons showed any key-unrelated pecking, regardless of whether they were apo or saline treated.

**Experiment 7: apomorphine autoconditioning**

The left section of Fig. 7 shows the mean pecking scores of the contingent and noncontingent groups in the first 10-min periods (0.1 mg/kg apo) and in the following 20-min periods (0.9 mg/kg apo) of the training session. Although the contingency group generally tended to peck slightly more than the noncontingency group, there were no significant differences on any of the five training days with regard to the 0.9 mg/kg periods [all $U$s $(8,8) \geq 24$]. On the first two days the 0.1 mg/kg period pecking of contingent and noncontingent groups did not differ significantly [day 1, 123 ± 68 vs. 98 ± 56 pecks/10 min; day 2, 141 ± 28 vs. 97 ± 32 pecks/10 min, both $U$s$(8,8) \geq 21$]. However, on days 3, 4, and 5, the pecking of the contingent group was significantly higher than that of the noncontingent group [day 3, 186 ± 41 vs. 61 ± 34 pecks/10 min; day 4, 175 ± 37 vs. 83 ± 30 pecks/10 min; day 5, 199 ± 47 vs. 100 ± 32 pecks/10 min, all $P$s $< 0.05$, $U$s$(8,8) \leq 11$]. These differences arose through the fact that between days 1 and 5 the pecking of the contingent group in the low-dose periods rose significantly from day 1 to day 6 [$P < 0.05$, $T(8) = 32$], whereas that of the noncontingent group did not [$T(8) = 19$]. Upon testing on day 6 after the sole administration of 0.1 mg/kg apo, the pecking in the first 10 min of the contingent group was significantly stronger than that of the noncontingent group [208 ± 50 vs. 56 ± 21 pecks/10 min, $P < 0.01$, $U(8,8) = 8$]. Similar results arose in the second 10-min period of pecking on day 6 [157 ± 15 vs. 74 ± 12 pecks/10 min, $P < 0.05$, $U(8,8) = 13$]. The lesser differences present in all the subsequent 10-min extinction periods were all nonsignificant [$U$s $(8,8) \geq 22$]. Although the pecking during the initial periods of the contingent group fell significantly from day 6 to day 7 [208 ± 50 against 131 ± 14 pecks/10 min, $P < 0.01$, $T(8) = 20$], the pecking of the noncontingent group differed only nonsignificantly [$T(8) = 32$].

**Fig. 7**



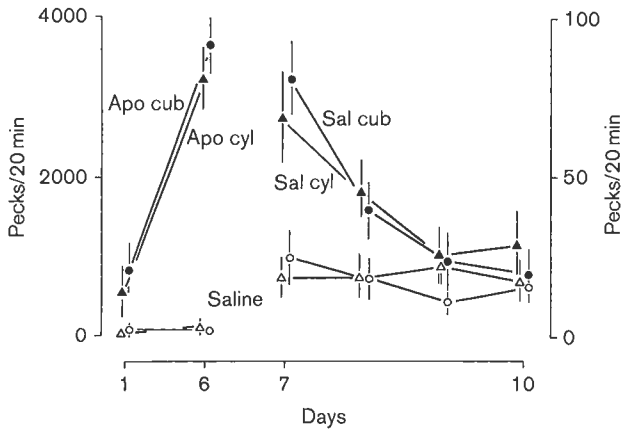

Experiment 7, apo autoconditioning. The mean ± SE pecking responses at a low dose (0.1 mg/kg)/high dose (0.9 mg/kg) of contingently (Cont, $n = 6$, ●) and noncontingently (Ncon, $n = 6$, ▲) treated pigeons. The left section of the figure (days 1 to 5) refers to the low-dose/high-dose training phase and the right section (days 6 to 8) to the low-dose-only testing phase. Note that different scales apply to the low-dose and the high-dose responding. Apo, apomorphine.

**Experiment 8: conditioned response context specificity**

As shown in Fig. 8 the pecking response of the two groups in the apo-contingent cages rose similarly and did not differ significantly at the end of the sensitization phase [day 6: 3641 ± 371 and 3232 ± 418 pecks/20 min, $U(6,6) = 14$]. The mean pecking responses in the saline-contingent cages fluctuated below 25 pecks/20 min in both groups. The initial responses shown under saline in the previously apo-contingent cages were significantly greater than those shown under the same conditions in the previously saline-contingent cages [day 7: 83 ± 13 vs. 24 ± 9, and 69 ± 16 vs. 18 ± 7 pecks/20 min, both $P$s $< 0.05$, $T(6) = 21$ and $T(6) = 19$]. There was no significant difference between the two groups of pigeons with respect to their responses in the previously apo-contingent and previously saline-contingent cages [all $U$s$(6,6) \geq 15$]. The responses under saline in the previously apo-contingent cages of both groups waned significantly over the next few days [day 10: 16 ± 7 and 29 ± 9 pecks/20 min, both $P$s $< 0.05$, $T(6) = 20$ and $T(6) = 21$]. By day 10, the responses shown in the previously apo-contingent cages by both groups were in fact not significantly different from those shown in the previously saline-contingent cages [both $T$s$(6) \leq 14$].

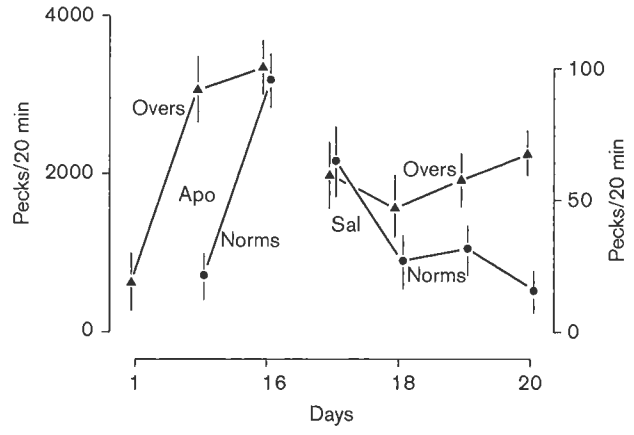
The broader issue of whether a CR was present and whether it was extinguished was further examined by pooling the scores of the two groups. The difference between the test scores in the previously apo-contingent and saline-contingent cages was significant on day 7 [$P < 0.01$, $U(12,12) = 28$] and day 8 [$P < 0.05$, $U(12,12) = 41$], but not on days 9 and 10 [both $U$s$(12,12) \geq 52$]. The fall in pecking from day 7 to day 10 was significant [$P < 0.01$, $T(12) = 70$]. All but one of the 12 pigeons

Fig. 8




Experiment 8, cage specificity of the conditioned pecking response. The mean ± SE pecking responses of two groups of pigeons ($n = 6$ each) that were sensitized to apo in either cubic white-walled, green-dotted cages (●) or in cylindrical black-walled, yellow-triangled cages (▲). The cages used were the same as those illustrated in Fig. 5. Concurrently, the pigeons were also exposed under saline to the alternative experimental cages (○, △). Only days 1 and 6 of this first phase are shown. In the second phase, days 7–10, both groups of pigeons were tested under saline in the previously apo-contingent cages (●, ▲) and in the previously saline-contingent cages (○, △). Note the different left and right time and response scales. Apo, apomorphine; cub, cubic; cyl, cylindrical; Sal, saline.

Fig. 9




Experiment 9, extinction resistance effect in apo-oversensitized pigeons. The mean ± SE pecking responses of an oversensitized group ($n = 8$, ▲) and a norm-sensitized group ($n = 9$, ●) during the sensitization phase (days 1 to 16, compressed scale) and the extinction phase (days 17–20, expanded scale). Note also that the left and right response scales differ. Apo, apomorphine; Norms, norm-sensitized group; Overs, oversensitized group; Sal, saline.

pecked more in the formerly apo-contingent cage than in the formerly saline-contingent cage on day 7; all but one of the 12 birds showed a decline in pecking from day 7 to day 10 in the apo-contingent cage, whereas only 7 of 12 did so in the saline-contingent cage.

To examine the relationship between the individual's sensitization increments (IRs) and CRs, the data from the six pigeons in this experiment that were first sensitized with repeated 0.5 mg/kg doses of apo in the white-walled, green-dotted cubic cages and then tested with saline in the same cages were pooled with those from another 19 pigeons that were treated identically in two other experiments (Acerbo *et al.*, 2003b, and Experiment 9 below); all these pigeons were of Konstanz stock. The SR (day 6) scores did not correlate significantly with the CR (day 7) scores (Spearman's correlation coefficient $r_s = 0.13$); the UR (day 1) and SR (day 6) correlation was also not significant ($r_s = 0.18$). However, the IR scores (day 6–day 1) did correlate significantly with the day 7 CR scores ($r_s = 0.43$, $P \leq 0.05$). This indicates that the IRs that accrued during the sensitization to apo were somewhat linked to the CRs obtained under extinction conditions, even though the SRs were not.

### Experiment 9: oversensitization and conditioned response

One of the pigeons in the oversensitized group became ill and died during the course of the experiment. Figure 9 shows the results relating to the remaining 17 birds. It is evident that both groups underwent marked sensitization. The pecking responses of the oversensitized and norm-sensitized groups at the final apo-sensitization session (day 16) were not significantly different [3350 ± 384 and 3216 ± 331 pecks/20 min, $U(9,8) = 31$]. On the first extinction session, both groups exhibited similar pecking responses [day 17: 59 ± 13 and 65 ± 15 pecks/20 min, $U(9,8) = 34$]. However, over the next few days the response of the norm-sensitized group declined significantly [day 20: 26 ± 10 pecks/20 min, $P < 0.01$, $T(9) = 42$; eight of nine birds evincing an overall decline in pecking scores]. The oversensitized group showed no significant decline over the four extinction sessions [day 20: 67 ± 8 pecks/20 min, $T(8) = 27$], with four birds exhibiting smaller decreases in pecking and five birds showing increases in pecking. On day 20, the response of the oversensitized group was in fact significantly higher than that of the norm-sensitized group [$P < 0.05$, $U(9,8) = 15$].

## Discussion

### Individual experiments

#### *Experiment 1: dose–response functions*

This experiment addressed the dose dependency of the apo sensitization. Although Basten-Krefft (1977) and Godoy (2000) had described the effects of repeated administrations of various doses of apo in pigeons, the design of these earlier studies was not fully adequate. The waxing and waning of the pecking response that follows the administration of a medium dose of apo agrees with time/effect courses that could be expected on the basis of the ~20-min half-life of apo found in mammalian neural tissue (Martres *et al.*, 1977). We note that

the test duration of 20 min that we have routinely used encompasses the attainment of the peak response rates regardless of the progress of sensitization (cf. Keller *et al.*, 2002; Braga *et al.*, 2009). It is remarkable that a single medium-dose of apo suffices to produce appreciable sensitization increments (cf. Bloise *et al.*, 2007). The sensitized responses to the various doses on day 6 cannot be understood as a simple progressive amplification of the response scores obtained with the doses on day 1. The day 1 (URs) dose–response curve rises steeply at doses above 0.1 mg/kg, but then levels off at about 1800 pecks/20 min at doses between 1.5 and 2 mg/kg apo; higher doses caused postural unbalances and retching reflexes, which diminish the pecking response (additional exploratory trials, data not shown). The day 6 responses (SRs) level off at pecking rates of about 3800 pecks/20 min at doses between 1 and 1.5 mg/kg apo and reduce again at doses above 2 mg/kg apo (exploratory trials, data not shown). A further ceiling effect arises through the fact that pigeons can physically sustain a maximal rate of about 1000 pecks/5 min for only short periods of time (Hörster *et al.*, 2003).

With regard to these dose–response data it must, however, be stressed that the pecking response elicited by any given dose of apo is modulated by the pigeon's stock of origin, by individual variability (see Experiments 2 and 3), and by the design of the testing environment, with strongly contrasting pecking targets augmenting the pecking response and a lack of such targets diminishing the response (Brunelli *et al.*, 1975; Basten-Krefft, 1977). The pecking responses are further affected by the adiposity of individual pigeons (apo being a markedly lipophilic substance), the time of day, the time of year, and environmental noises, including infrasound (own unpublished observations; Yodlowski *et al.*, 1977). Despite all of these factors, the sensitization effect (SR) has proven to be an extremely robust finding across all of our studies. Moreover, once established, the sensitization to apo persists without any appreciable decay for 2 or 3 weeks and with some progressive decay for up to at least 2 years (Keller *et al.*, 2002).

### *Experiment 2: stock differences*

The experiment confirmed earlier observations (Basten-Krefft, 1977; Wynne and Delius, 1995) that Bochum stock and Konstanz stock pigeons differed in the degree of responsiveness to apo, in terms of both URs and SRs. Nevertheless, both sets of pigeons evinced clear-cut response increases (IRs) with the difference that Bochum pigeons reached near-asymptotic responding on about the third apo treatment, whereas the Konstanz pigeons did so only on about the fifth apo treatment. Note, however, that the differences found could be due to regional differences in husbandry or in genetic composition between the stocks (cf. Ellenbroek *et al.*, 2005).

### *Experiment 3: selected parentage*

The results show that, although there was some regression to the mean, the offspring of apo-unresponsive pigeons were in turn low responders and that the offspring of apo-responsive pigeons were in turn high responders, with the offspring of mixed apo-responsiveness pigeons being intermediate responders (cf. Cools, 1994). However, even the unresponsive offspring group showed traces of sensitization and conditioning. The overall results support the view that differences in apo responsiveness of pigeons have a genetic background. It is worth pointing out that in both experiments the groups that pecked the least during day 1 of the apo-sensitization procedure also exhibited a lesser response increase until day 6, and also pecked less on day 7 when challenged with saline instead of apo. This is in agreement with the results of experiments in which a reduction of the day 1 response to apo brought about by coadministration of dopamine antagonists was correlated with a lesser response increment until day 6 and a smaller response after saline-only treatment on day 7 (Acerbo *et al.*, 2003a; Acerbo and Delius, 2004; see also Discussion of Experiment 8). Differences in apo sensitivity have also been found in domestic fowl strains selectively bred for spontaneous high and low frequencies of pecking at cage-mate feathers (allopecking; Van Hierden *et al.*, 2005; Kjaer, 2009). It could be that similar genetic polymorphisms of dopaminergic receptors to those found in fowl (Flisikowski *et al.*, 2009) might also exist in pigeons. We note incidentally that apo-treated pigeons sometimes direct some of their pecks at companion pigeons, when available.

### *Experiment 4: sensitization context specificity*

Burg *et al.* (1989) suggested that the sensitization to apo was context dependent, in the sense that the IR that had been induced in one kind of distinctive experimental cage did not transfer to a markedly different kind of experimental cage. The present results clearly demonstrated this in Bochum stock pigeons, thus extending equivalent findings with Konstanz stock pigeons (Godoy and Delius, 1999; Acerbo *et al.*, 2003a, 2003b). The results also concur with those obtained by Keller *et al.* (2002) with a very differently designed experiment. The lack of transfer of sensitization from one environmental context to another supports the hypothesis that apo sensitization in pigeons involves a conditioning process. In view of the results reported next, it must be stressed though that a nontransfer outcome only arises in pigeons when the cage environments used are thoroughly different from one another. When the two experimental cages utilized are not radically different, a partial transfer can arise through a simple stimulus generalization process (Godoy and Delius, 1999). The fact that saline pretreatment in the cubic cages did not curtail the subsequent apo sensitization in the same cages confirms that latent

inhibition plays no role in the latter process (Godoy and Delius, 1999; Acerbo *et al.*, 2003b).

***Experiment 5: sensitization in darkness***

The pecking of pigeons is a prominently diurnal and visually guided behavior pattern (Zeigler *et al.*, 1995; Hörster *et al.*, 2002); the pecking induced by apo, although an artificial motor stereotypy, is also importantly controlled by visual stimuli (Brunelli *et al.*, 1975; Basten-Krefft, 1977; Keller and Delius, 2001). It is, however, known that apomorpine pecking does occur in darkness (Brunelli *et al.*, 1975; Delius, 1985; Pinkston *et al.*, 2008). Here we confirmed that the dark condition does not prevent apo-induced pecking – although eliciting chiefly floor pecking rather than mainly wall pecking – and that darkness supports the development of a sensitization that amounts to about half of that attained by the pigeons starting under the light condition. More to the point though, on switching from the light condition to the dark condition the apo pecking response fell to about half of its previous magnitude. The visual degradation of the $CS_{cage}$ thus had an important suppressive effect on the $SR_{apo}$ pecking. The remaining partial response transfer is likely to have been caused by a straight stimulus generalization (Godoy and Delius, 1999) inasmuch as the cage was nonvisually the same under both lighting conditions.

***Experiment 6: apomorphine–saline discrimination***

The results showed that the pigeons could learn to distinguish between the internal states that were induced by the apo or saline administrations. This agrees with the results obtained by Järbe (1984) in similar experiments using higher doses of apo, although we are uncertain how he prevented the indiscriminate pecking induced by such doses from interfering with the required discriminative key pecking. The relatively low dose of apo we used totally circumvented this issue, as observations showed that there was no key-unrelated pecking during the critical initial six trials of the test sessions. Food-seeking behavior appeared to suppress any pecking induced by the 0.25 mg/kg apo dose, at least momentarily. However, the low apo dose used might have been responsible for the fact that, judging by the choice behavior, our pigeons occasionally confused the apo state that they were nominally in with the saline state that they were not in. Nevertheless, the overall result supported the notion that an interoceptive apo state could potentially act as a conditioning stimulus ($CS_{apo}$) in a classical conditioning procedure.

***Experiment 7: apomorphine autoconditioning***

That a weak foot-shock, which initially causes no detectable behavioral response, comes to elicit a marked escape response in rats when it is repeatedly followed by a strong foot-shock has often been demonstrated in the course of conditioning practicals (J.D. Delius, unpublished observations; cf. Colavita and Szeligo, 1971, brain stimulation in cats). Pharmacologically it has been shown that a low dose of dopamine occasioning a negligible rise in blood pressure can serve as a CS that comes to support a sizeable CR blood pressure rise when the low dose has previously been repeatedly followed by a high dose of dopamine (US) leading to a large blood pressure rise (UR; Dworkin and Dworkin, 1995). The results reported here suggest the incidence of an analogous autoconditioning with apo treatments: an initially rather minor pecking response to the 0.1 mg/kg apo dose, acting as the CS, increased (IR) as the training progressed in the CS–US contingency group but not in the noncontingency group. The development of a CR was demonstrated in subsequent test sessions: the administration of the same 0.1 mg/kg dose yielded a significantly larger response in the contingency group than in the noncontingency group and was subsequently extinguished in a typical CR manner.

The fact that the $CR_{apo}$ obtained, although significant, was comparatively minor requires comment. To begin with, the 0.1 mg/kg apo CS was probably barely above the pigeon's apo detection threshold (see Experiments 1 and 6). Furthermore, according to the data presented in Fig. 2, this low dose of apo, on its own, could have been expected to yield much less pecking than that actually elicited on day 1 of the present experiment; however, it in fact yielded significantly more pecking than in Experiment 1 [$110 \pm 59$ vs. $4 \pm 11$ pecks/10 min, $P < 0.01$, $U(7,12) = 11$]. Note, however, that all the pigeons of the present experiment had been presensitized with repeated 0.9 mg/kg apo treatments before being subjected to the first 0.1 mg/kg treatment. Godoy *et al.* (2000) reported that in pigeons presensitized with a higher dose of apo (1.0 mg/kg) a lower apo dose (0.2 mg/kg) yielded an appreciably higher response than it did in non-presensitized pigeons. Accordingly, the above difference was to be expected. It is thus all the more remarkable that the 0.1/0.9 mg/kg apo contingency pigeon group exhibited a significant further increase in response to the low dose, whereas the noncontingency group did not. Incidentally, the subsequent extinction of that modest pecking CR is the only instance of a clear-cut development of tolerance to repeated apo administrations that we have ever obtained.

***Experiment 8: conditioned response context specificity***

Lindenblatt and Delius (1987) had observed that the CR that emerges when previously apo-sensitized pigeons are treated with saline and placed in the corresponding experimental cage is markedly context dependent. The present results confirm that, before the response extinction set in, an above-control level of conditioned pecking was only expressed in the cage to which the pigeons had previously been exposed under apo, and not in the cage to which they had been exposed under saline. That is,

the CR pecking was strictly specific to the cage context in which the pigeons had previously experienced the effect of apo. As this fully concurs with similar findings reported previously (Lindenblatt and Delius, 1987; Wynne and Delius, 1995; Godoy and Delius, 1999; Keller and Delius, 2001; Acerbo *et al.*, 2003a), the $CR_{cage}$ specificity can be considered quite robust. The results also confirm that the CRs are relatively minor compared with the equally environment-specific IRs obtained during the sensitization. This difference in magnitude is accounted for by the circumstance that, although the IR is a response conditioned to the $CS_{apo \times cage}$ compound, the CR is only a response to the $CS_{cage}$ component.

As the $CS_{cage}$ is also part of the $CS_{apo \times cage}$ compound, there should be some correlation between the individual CRs and IRs, which is in fact what we found. Amphetamine and cocaine sensitization studies in rats (Crombag *et al.*, 2001; Hotsenpiller and Wolf, 2002) have reported that there is no linkage between SRs and CRs, and indeed we found the same to be true here for the pigeons' responses to apo. We believe, however, that in view of the individual differences in apo sensitivity (cf. Experiment 3) the SR scores alone are not suitably representative of the sensitization undergone by individual pigeons, this being better captured by the IR scores. Note too that the outbred pigeon stock that we used was probably more heterogeneous in apo responsiveness (cf. Experiment 3) than the relatively inbred rat strains used in the above-mentioned studies.

### *Experiment 9: oversensitization and conditioned response*

Apart from being of a markedly smaller magnitude than the IRs, the CRs have been generally found to be susceptible to relatively rapid extinction (Experiments 3 and 8; Godoy and Delius, 1999; Acerbo and Delius, 2004). It is known, however, that in more conventional conditioning preparations an overtraining, although not yielding an augmented CR, often leads to a relative resistance to extinction of the CR (Williams, 1938; Perin, 1942). Here we showed that an oversensitization treatment of 16 days rather than the norm-sensitization of 6 days yielded a similar longer-lasting, that is, extinction-resistant, CR, although leading neither to a larger SR (cf. Wynne and Delius, 1995) nor to a larger CR. It would have been instructive to prolong the extinction phase to see when the CR of the oversensitized group would begin to wane, but that was unfortunately not done. Regardless, however, much as with overtraining in conventional conditioning preparations, oversensitization with apo appears to lead to a more extinction-resistant CR pecking compared with norm-sensitization. However, an attempt to induce an augmented and persistent CR through an intermittent apo-sensitization/saline extinction regime was unsuccessful (M.J. Acerbo and S. Iskra, unpublished experiment).

### Conditioned sensitization

As already mentioned in the Introduction section, the sensitization that develops upon repeated administration of certain drugs, prominently dopaminergic drugs, has been variously attributed to a number of different pharmacokinetic and pharmacodynamic processes (Stewart and Vezina, 1991; Stewart and Badiani, 1993; Tirelli and Heidbreder, 1999; Zavala *et al.*, 2000; Crombag *et al.*, 2001; Anagnostaras *et al.*, 2002; Domjan, 2005). Concerning the sensitization of pigeons to apo, we have found all of these accounts to be at least partially unsatisfactory and have thus striven to develop a better-fitting alternative explanation.

Experiments carried out in our laboratory have consistently shown that in pigeons the sensitization, or more precisely the IR, that develops upon repeated administration of apo is strongly cage-environment specific (Experiment 4; Burg *et al.*, 1989; Godoy and Delius, 1999; Keller and Delius, 2001; Acerbo *et al.*, 2003a; cf. also Akins and Geary, 2008, cocaine in quail). This context specificity also applies to the CR recorded when pigeons previously sensitized to apo are subsequently tested under the influence of only saline (Experiment 8; Lindenblatt and Delius, 1987; Wynne and Delius, 1995; Godoy and Delius, 1999; Keller and Delius, 2001). Note, however, that for the demonstration of cage specificity it is essential that the cages used as controls be physically markedly different from those used for the sensitization procedure to avoid a cross-transfer effect due to simple stimulus generalization (Experiment 6; Godoy and Delius, 1999). Several different control treatments have indicated that the marked context dependency is not due to any simple differential behavioral habituation or sensitization to the experimental cages or procedures (Experiments 4 and 8; Godoy and Delius, 1999; Keller and Delius, 2001; Acerbo *et al.*, 2003a).

The context specificity found suggests that an account based on classical Pavlovian conditioning is probably applicable. Within this account, the administration of apo is viewed as a US that elicits a UR. When pigeons repeatedly experience a particular experimental cage under the influence of apo, this context comes to function as a CS. The repeated CS/US pairings lead to the development of a pecking IR. A waxing IR pecking adds to the UR pecking to constitute the total sensitized pecking response (SR = UR + IR). However, the mean pecking IR that arises during the sensitization treatment is considerably stronger, by a factor of about 50–100 times, compared with the mean CR obtained during subsequent testing when the pigeons received saline instead of apo and were placed in the sensitization cage CS/~~US~~ (= CS/no US) condition (Experiments 3 and 8; Lindenblatt and Delius, 1987; Wynne and Delius, 1995; Godoy and Delius, 1999; Keller and Delius, 2001; Delius *et al.*, 2002; Acerbo *et al.*, 2003a, 2003b; Acerbo and Delius, 2004). Attempts to augment the magnitude of

CRs through procedural modifications have not been successful (Experiment 9; unpublished experiment).

The context specificity and weak CR results are explained by assuming that the CS effective during the sensitization course is a compound of an exteroceptive ($CS_{cage}$) and an interoceptive ($CS_{apo}$) component – in other words, by supposing that not only the cage environment but also the apo administration itself has CS properties. It has been demonstrated that apo induces a drug-specific state that can be sensed by pigeons (Experiment 5; Järbe, 1984; cf. Johanson and Barret, 1993; Carey *et al.*, 2005). We have furthermore shown that apo administration can indeed function as a $CS_{apo}$ supporting a pecking CR when a small dose of apo repeatedly precedes a large dose of apo (Experiment 7: autoconditioning). Nowadays it is widely believed that a US often also acts as a collateral CS in classical conditioning (Bouton, 1993). Accordingly, we hypothesize that the sensitization IR is caused by an interactive $CS_{cage \times apo}$ component – that is, it effectively is a $CR_{cage \times apo}$ component – whereas the test CR reflects the effect of the $CS_{cage}$ component alone, thereby effectively being a $CR_{cage}$ component. In other words, the IR is conjunctively state and context dependent, whereas the CR is only context dependent (Stephens *et al.*, 2000). The assumption of an approximately multiplicative, that is, conjunctive, interaction between the two components suggests itself because the $CS_{apo}/\cancel{US}$ not accompanied by the $CS_{cage}$ – that is, an apo challenge in a cage different from that used during sensitization – yields at best a very minor pecking $CR_{apo}$, which is mostly difficult to detect because of the somewhat variable and inevitably copresent $UR_{apo}$ (Experiment 4; Godoy and Delius, 1999; Keller and Delius, 2001; Keller *et al.*, 2002). Note also that any presumed $CR_{apo}$ is difficult to distinguish from a fractional IR because of stimulus generalization – that is, because of some similarity between the sensitization and test cages. Conversely, and as already stated, the $CS_{cage}$/no $CS_{apo}$ condition elicits a minor pecking $CR_{cage}$. The circumstance that two different stimuli in some cases can only be fully effective as a CS when occurring conjunctively (as a configuration), but not when occurring separately (as single elements), is a widely recognized fact in the conditioning literature (Domjan, 1997; Pearce, 1997).

Although we assume, largely on the basis of the outcome of Experiment 6, that apo acts as an interoceptive CS, we must acknowledge that when pigeons peck under the influence of apo they generate concomitant sounds through substrate contacts (Schall and Delius, 1991; Experiment 5 here). It is possible that these pecking noises could function as an apo-related exteroceptive CS. However, Keller (2001) reported that, in an experiment designed much as the present Experiment 5 but using, instead of visual cues, pulsing noise versus white noise as discriminatory stimuli, none of four pigeons showed a sound-specific pecking IR or CR. Sounds, therefore, do not appear to be effective as context CS in pigeon apo sensitization. However, this negative result could have arisen because the acoustic stimuli were overshadowed by simultaneously present nondiscriminatory visual stimuli (cf. Domjan, 1997); sounds may still prove to be an effective CS if presented in the dark (cf. Experiment 4) or in a peck-contingent manner (cf. Delius, 1985).

There is no evidence that latent inhibition – that is, $CS/\cancel{US}$ presentations depressing subsequent CS/US conditioning – plays any role in pigeon apo sensitization. The development of sensitization instituted in a cage to which the pigeons have been repeatedly pre-exposed without being administered apo – it can even be their very familiar home cage – is closely similar to that instituted in a cage that is totally novel to them (Experiment 4, Wynne and Delius, 1995; Godoy and Delius, 1999; Keller *et al.*, 2002; cf. Lubow, 2010). Along the same lines, once a sensitization is established in pigeons, the IR does not extinguish upon repeated under-saline exposures to the training cage even though the CR normally does so upon repeated exposures to the training cage (Experiments 3, 8, and 9; Godoy and Delius, 1999). The explanation is that both the latent inhibition treatment and the extinction treatment involve repeated exposures to the $CS_{cage}/\cancel{US}$ condition relevant for the CR, rather than repeated exposures to the $CS_{apo \times cage}/\cancel{US}$ condition relevant for the IR, a treatment that is in fact nearly impossible to implement because of the dual CS and US role of apo. It would be informative to repeatedly treat pigeons with the $CS_{cage}/\cancel{US}$ condition, then sensitize them with an interspersed course of $CS_{apo \times cage}$/US treatments, and finally test them under the $CS_{cage}$ condition. The pecking CR of such pigeons would presumably be depressed in comparison with unpretreated pigeons sensitized with the course of $CS_{apo \times cage}$/US treatment alone and then tested under the $CS_{cage}$ condition; the sensitization IRs of both groups should, in contrast, be equivalent. Concerning both the IR and the CR, it may be important to differentiate between an extinction of action (pecking response) and an extinction of taxis (response targeting), following a distinction made by early ethologists (Tinbergen, 1951). Using a differentiation (i.e., discrimination) counterconditioning procedure $CS_1^+$/US, $CS_2^-/\cancel{US}$, followed by a reversal procedure $CS_2^+$/US, $CS_1^-/\cancel{US}$, Keller and Delius (2001) obtained evidence that the initially acquired IR and CR selective pecking aimed at a $CS_1$ (e.g., red triangles on a black background) that was extinguished when the subsequent above-mentioned reversal brought about pecking aimed at a $CS_2^+$ (e.g., green circles on a white background).

An alternative account of the sensitization to apo in pigeons can be derived from the apo autoconditioning demonstrated in Experiment 7. When a larger apo dose is intramuscularly injected, the apo brain titer will necessarily go through an initial and transitory lower titer phase followed by a later and longer higher titer phase that, when repeated over days, would tend to emulate the autoconditioning paradigm used in that experiment. Might thus the IR underlying the SR generally be nothing more than a cumulating CR to a $CS_{apo\ low}$ brought about by the repeated $CS_{apo\ low}$–$US_{apo\ high}$ contingency? The fact that during apo sensitization the pecking SR begins ever earlier agrees with the notion that the initial low levels of apo come to support the development of a CR (cf. Fig. 1; Wynne and Delius, 1995). By itself, this process would not yield cage-context-dependent IRs and CRs (Experiments 4 and 8), but if the cage context functioned as a so-called occasion setter (Schmajuk and Holland, 1998), ensuring a context-conditional autoconditioning, it would. This explanation is not really different from the one expounded above, but it helps to understand why latent inhibition and response extinction do not affect the apo IR. In any case, it remains to be determined whether the autoconditioning to apo is a reliable and robust effect.

Stimuli that function as appetitive US, that is, as stimuli that evoke approach responses within Pavlovian conditioning, as a rule also function as appetitively reinforcing stimuli – that is, as rewarding stimuli – within instrumental conditioning. Apo conforms with this rule, inasmuch as it has been shown that rats and monkeys will learn to self-administer small doses of intravenous apo by lever-pressing (Baxter *et al.*, 1974; Woolverton *et al.*, 1984). We have not been able to complete intravenous apo self-administration experiments with pigeons, with canullar clogging in birds being a more pronounced problem than in mammals (J.D. Delius, unpublished), but intraperitoneal self-administration might be a viable alternative technique. However, the rewarding effect of apo administrations has been demonstrated in pigeons using the place preference procedure. Burg *et al.* (1989), using a Y-maze with two differently decorated goal cages, showed that pigeons that had been repeatedly injected with apo in one goal cage and with saline in the other one showed a marked preference to move into the apo-associated cage when later allowed to choose while untreated (cf. Schechter and Calcagnetti, 1993; Levens and Akins, 2001). It is thus possible that repeated apo treatments in pigeons lead to an incentive sensitization – an increased seeking/wanting of the drug (Robinson and Berridge, 2008) – but this particular issue requires further investigation (cf. Deroche *et al.*, 1999; Yager and Robinson, 2013).

### Model generality

Whether the above conditioning model could also apply to the sensitization to apo and even to the much more extensively studied sensitization to amphetamine and cocaine – or indeed to the less amply examined sensitization to apo – in mice and rats is a complex issue. Before proceeding, it is appropriate to stress that such an attempted equation is likely to be inherently difficult. As far as amphetamine and cocaine are concerned, these are far less specific dopamine agonists compared with apo and are, furthermore, drugs acting presynaptically rather than postsynaptically. The species differences cannot be ignored either, beginning with the fact that the most salient response to apo is pecking in pigeons, whereas the response to all three drugs is locomotion in rodents. Differences in experimental designs and procedures are certain to add diversity. Equations with other, alternative conditioning accounts of sensitization that have been proposed are often scabrous because the relevant accounts are frequently couched in nonstandard and not particularly well-defined terms (cf. Ahmed *et al.*, 1996).

Because the literature on the sensitization to psychostimulants in rodents is vast and riddled with contradictory findings, we focus here on what is probably the most coherently unified series of studies by Robinson and colleagues (Anagnostaras and Robinson, 1996; Crombag *et al.*, 1996, 2000, 2001; Badiani *et al.*, 1997; Browman *et al.*, 1998a; Robinson *et al.*, 1998; Anagnostaras *et al.*, 2002). They examined the rotational locomotion of unilaterally substantia nigra, 6-hydroydopamine-lesioned rats or the straight locomotion of intact rats activated by amphetamine or cocaine administration. Their findings – which partially differ from ours in pigeons – are as follows: (a) the behavioral response (UR) to a first drug injection (US) is stronger in a novel distinct cage than in a familiar distinct cage or indeed absent in the very familiar home cage; (b) the SR, which develops through repeated drug administrations, reaches a similarly sized asymptote in a novel distinct cage as in a somewhat familiar distinct cage, but sensitization does not develop at all in a very familiar cage (but see Matos *et al.*, 2010, nonlesioned rats, apo), although it does when a higher psychostimulant dose is used (Browman *et al.*, 1998b; Li *et al.*, 2004); (c) the CR shown is the largest in the distinct cage in which the sensitization treatment takes place, less in a different distinct cage, and even completely absent in the home cage; (d) the IR that develops during sensitization in one distinct cage also partially shows up in another distinct cage, in some cases at least, but not in the very familiar home cage; (e) the magnitude of the CR upon a subsequent saline challenge is weaker (Anagnostaras and Robinson, 1996; Crombag *et al.*, 2001; but see Carrera *et al.*, 2013) than the IR that accrues during the preceding sensitization; (f) moreover, the magnitude of the CRs expressed by individual rats does not correlate with the magnitude of the SRs (= URs + IRs) achieved by the same rats; and (g) the CR is markedly susceptible to extinction, whereas the IR is not, when repeated $CS_{cage}$/~~US~~ exposures are

used. We note though that Carrera *et al.* (2013) lately entertained a conditioning account of apo sensitization in rats that appears to be quite akin to the one we propose. Moreover, they report having obtained excitatory and inhibitory effects with, respectively, high and very low (dopamine autoreceptor effective) 0.01 mg/kg apo doses (cf. Deviche, 1985, pigeons) in treatments that could correspond to trace conditioning trials (Domjan, 1997), an issue that we have not examined.

Concerning the above items (a)–(d), all of which refer to the fact that cage familiarity appears to attenuate the UR, IR, and CR effects of psychostimulants in rats, Browman *et al.* (1998b; cf. Badiani *et al.*, 1997; Carey and Damianopoulos, 2006) assume that, for rats, a novel cage environment induces an arousal occasioning stress that augments the sensitivity to psychostimulants. Anagnostaras *et al.* (2002) favored the hypothesis that by a familiarization treatment a cage environment may come to function as an inhibitory occasion setter (Schmajuk and Holland, 1998) for sensitization to the drug, a process that they tentatively assumed to be based on nonassociative conditioning. However, the experiment that they adduced in support of this hypothesis did not really test it (Domjan, 2005; compare also Ahmed *et al.*, 1996; Adams *et al.*, 2000). A simpler explanation for why rats show no sensitization when psychostimulant-treated in their familiar home cage (Fraioli *et al.*, 1999; Crombag *et al.*, 2001) may be that rats – differently from pigeons in similar contexts – are affected by a latent inhibition effect, whereby repeated exposure to the $CS_{cage}/\cancel{US}$ condition leads to a nonovert inhibitory CR, which subsequently hinders the development of an excitatory CR (Domjan, 1997; cf. Lubow, 2010).

None of the sensitization-enhancing effects of context novelty listed above as items (a)–(f) have been observed in apo-treated pigeons. A prefamiliarization with the distinct experimental cage in which the sensitization to apo takes place has no sizeable effect upon the pecking URs and IRs obtained (Experiment 4; Godoy and Delius, 1999; Acerbo *et al.*, 2003a). Indeed, Wynne and Delius (1995) found that sensitization treatments effected in the very familiar home cage yielded, if anything, a larger IR and a more pronounced CR than a sensitization treatment effected in an unfamiliar distinct experimental cage. The explanation for this species difference in the influence of novelty and familiarity, if it really exists, could be based on the pronouncedly different environmental conditions to which homing pigeons and laboratory rats are adapted.

With regard to the above items (d) and (e), we need to consider whether the assumption of a configural, multiplicative $CS_{apo \times cage}$, which we found to agree well with the pigeons' results, also conforms with the findings in rats or whether the assumption of an additive $CS_{apo} + CS_{cage}$ scheme is more fitting for the latter. Concerning visual stimuli – although not olfactory stimuli – it is likely that rats are less prone than pigeons to compound elementary stimuli into configural stimuli (Delius and Delius, 2006). Applied to the psychostimulant sensitization of rats, this difference in disposition would entail that they would show only a partial context-dependent sensitization, as itemized above under (b). The additive scheme, however, implies that the CR shown by rats should not be overly context dependent which, according to item (c), is the case. However, it is possible that the CR transfer between distinct cages observed in rats might be due to some degree of stimulus generalization. That is, the response transfer might be attributable to some perceived similarity between the test cages. We have previously suspected (Godoy and Delius, 1999) that odor cues, to which rats are known to be highly sensitive, could have promoted generalization, but Crombag *et al.* (2000) have reported that this factor is unlikely to play a role.

It seems possible that, in rats, the two CS components of interest interact in a mixed multiplicative and additive manner – for example, $CS = 0.5\ (CS_{drug \times cage}) + 0.5\ (CS_{drug} + CS_{cage})$. Both the additive and multiplicative features imply that the CR – the response under the $CS_{cage}/\cancel{US}$ condition – should be of a smaller magnitude than the IR – the response under the $CS_{drug}$, $CS_{cage}$/US condition. However, the fact that in rats the CR is frequently markedly smaller than the IR (but see Carreras *et al.*, 2011) suggests that the multiplicative scheme is also partially operative. The resistance to extinction of the IR shown by rats upon repeated $CS_{cage}/\cancel{US}$ exposures [item (g); cf. Anagnostaras and Robinson, 1996; Crombag *et al.*, 2001; see also Tirelli *et al.*, 2005] similarly requires that they at least partially rely on the multiplicative $CS_{drug \times cage}$ component that is not affected by this extinction treatment. Note, however, that as the $CS_{cage}$ component plays a role in eliciting both the IR and the CR regardless of the above schemes, one would expect some correspondence between the magnitudes of the two responses. However, Crombag *et al.* (2001), item (f) above, reported the absence of any correlation between the individual SRs (= URs + IRs) and CRs in amphetamine-treated rats. In apo-treated pigeons, we also found no significant correlation between individual SRs and CRs but found instead that individual IRs – arguably a better index of conditioning than SRs – and CRs did yield a significant correlation.

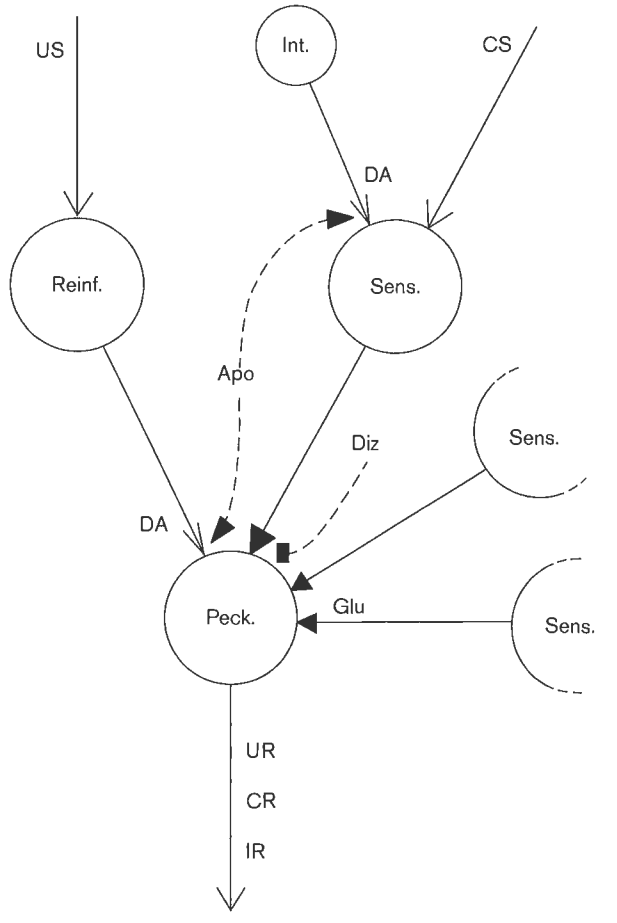
### Neural model

Classical conditioning learning is currently ascribed to a neurophysiogical long-term potentiation process known to occur in many glutamatergic synapses of vertebrate brains (Kandel *et al.*, 2013). This potentiation involves increments in synaptic efficacy that are initiated by the coactivation of the postsynaptic molecular *N*-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid glutamate receptors, which leads to an

upregulation and even a multiplication of AMPA receptors (cf. Sutton *et al.*, 2003; Wolf and Ferrario, 2010). In many glutamatergic synapses, the potentiation of glutamatergic transmission has been found to be importantly facilitated by heterosynaptic coactivation of D1 and D2 dopamine molecular receptors (Centonze *et al.*, 2001; Gore and Zweifel, 2013). The conditioning that is supported by this neural arrangement is nevertheless attributable not to a dopaminergic but rather to a lasting increase in glutamatergic transmission, which may even involve synaptic growth and multiplication. Concerning the sensitization to apo in pigeons, we have found that coadministration of the NMDA receptor antagonist dizocilpine does indeed block the development of the context-dependent apo IR and also hinders the expression of a context-dependent CR (Acerbo *et al.*, 2003b; see also Zarrindast *et al.*, 2003; cf. Battisti *et al.*, 2000). This finding led to the hypothesis that sensitization to apo in pigeons is also based on an alteration of glutamatergic transmission mechanisms and not primarily on an alteration of dopaminergic transmission (Acerbo *et al.*, 2003a, 2005; Acerbo and Delius, 2004; cf. Dias *et al.*, 2010).

It is thus possible to consider a neural model of the sensitization to apo that embodies the previously presented conditioning account. We recur to a neural mechanism originally suggested by Wickens (1990) (see also Reynolds and Wickens, 2002) to account for sensorimotor learning in rats, and propose that it could explain the context-dependent sensitization to apo in pigeons (Delius *et al.*, 2002). Wickens (1990) drew attention to the fact that dopaminergic nigrostriatal/tegmentostriatal projections conveying reinforcement signals converge with glutamatergic corticostriatal pathways conveying stimulus signals to the ventral striatum. These inputs are known to interact synaptically in the manner outlined above, such that a contingent activation of both these pathways during conditioning strengthens glutamate-mediated transmission. The ventral striatum is known to be the origin of motor pathways mediating behavioral responses. We assume that, in sensitization, apo mimics the activation of the nigrostriatal/tegmentostriatal pathway at the ventrostriatal level and triggers the pecking responses. This arrangement constitutes the US–UR link that was postulated earlier. The $CS_{apo \times cage}$ combination is assumed to selectively activate a corticostriatal glutamatergic pathway that is specifically responsive to the particular CS combination (Fig. 10). There is ample evidence for the presence of intrinsic dopaminergic neurons in sensory systems and particularly so in the visual system (cf. Noudoost and Moore, 2011), for example, at the retinal level (Brown and Makman, 1973; Djamoz and Wagmer, 1992; Rohrer and Stell, 1995; Witkovsky, 2004), where they are importantly involved in the visual dark adaptation process. It is bound to be activated by apo administrations and could mediate the

**Fig. 10**




Neural model of sensitization to apo. Apo, apomorphine (narrow, filled arrowheads); CS, conditioning stimulus; CR, conditioned pecking response; DA (narrow, open arrowheads), dopaminergic synapses; Diz, dizocilpine (bar ending); Int., sensory-intrinsic dopaminergic neuron; IR, incremental pecking response; Glu (wide, filled arrowheads), glutamatergic conditionable synapses; Peck., ventrostriatal motoric pecking neuron; Sens., sensory neurons; US, unconditioned stimulus; Reinf., nigrotegmental reinforcement mediating neuron; UR, unconditioned pecking response; wide unfilled arrowheads, unspecified neurotransmitter synapses.

$CS_{apo}$ component of the effective $CS_{apo \times cage}$ compound in pigeons. The temporally contingent activation at the ventrostriatal level of $CS_{apo \times cage}$-driven glutamatergic synapses and $US_{apo}$-driven dopaminergic synapses would then lead to the strengthening of the $CS_{cage \times apo}$–IR link. Although by no means undisputed, neural models of this same general type for context-dependent sensitization have recently gained favor (cf. Carrera *et al.*, 1998; Kelley, 1999; Bell *et al.*, 2000; Kelley 2004; Hernandez *et al.*, 2005; Lapish *et al.*, 2006).

It must be stressed that it is nowadays permissible to at least partially equate bird brains with mammalian brains concerning this model. Although regarded until recently as lacking a cerebral cortex, birds have been shown to

possess an analogous – if not homologous – forebrain structure (Reiner *et al.*, 2004). It has also been demonstrated that the avian ventral striatum/accumbens area is glutamatergically innervated (Acerbo *et al.*, 2002). There is similarly ample evidence that the ventral tegmental area and the substantia nigra of birds innervate the basostriatal structures dopaminergically, much as they do in mammals (Durstewitz *et al.*, 1998; Reiner *et al.*, 2004; Bálint *et al.*, 2011). Naturally, the proposed model is schematic: the real network is certain to involve several further neural structures (Delius, 1985; Lindenblatt and Delius, 1988; Wynne and Delius, 1996; cf. Nelissen *et al.*, 2012).

The avian neural substrate that mediates the sensitization to apo might possibly be reducible to a ventral forebrain slice preparation (Delius *et al.*, 2002; cf. Farries and Perkel, 2000; Stuber *et al.*, 2011). The efferences corresponding to pecks (UR, IR, and CR) can be expected to be reflected in ~3 Hz volleys of neural activity (Hörster *et al.*, 2003); the US could consist of brief perfusions with apo and the CS could be the electrical stimulation of afferent corticobasal pathways. This would represent a preparation suitable for a more detailed study of the neurochemical processes underlying the stimulus context-dependent sensitization and, more generally, the processes underlying sensorimotor conditioning.

### Addiction

Neither in the course of the experiments reported here nor in the course of the many other experiments that we have performed using apo have we ever come across any evidence of apo-treated pigeons becoming addictively dependent on apo, by showing, for example, some analog of the wet-dog shakes of morphine-addicted rats upon drug withdrawal. Indeed, apo in the past has been considered incapable of causing addiction in humans, but, as already remarked, more recently a few cases of addiction have been reported as arising in the course of prolonged apo self-therapy for Parkinson's disease (Téllez *et al.*, 2006). The case reported by Téllez and colleagues indicates that the apo abuse only developed after a lengthy period of apo intake, and suggests that it was connected with some loss of the relieving/pleasurable effect of the prescribed apo dose (cf. Strakowski *et al.*, 2001, amphetamine in humans). The augmented intake of apo appears to have followed the development of tolerance; whether there might (also) have been a separate increase in the incentive value of the drug (Stuber *et al.*, 2011; Saunders and Robinson, 2013; Yager and Robinson, 2013) seems uncertain. There is evidence that protracted self-administration is necessary for the development of proper addiction to psychostimulants in rats (Heyne and Wolffgramm, 1998; Jacobs *et al.*, 2003). During the course of such prolonged administrations, sensitization to drugs may be only an initial, relatively rapid process (cf. Phillips and Di Ciano, 1996; Katzenschlager *et al.*, 2005) that is eventually followed by a delayed and slow-developing tolerance (Emmett-Oglesby *et al.*, 1993; Mendelson *et al.*, 1998), which may constitute the basis for the onset of addictive behavior (cf. Deroche-Gamonet *et al.*, 2004; Ben-Shahar *et al.*, 2005). It would be instructive to switch to a self-administration rather than experimenter-administration procedure (cf. Ahmed, 2010; Calipari *et al.*, 2014) and to prolong the apo treatment of pigeons to several months rather than the maximal 3 weeks that we have implemented so far (cf. Marusich *et al.*, 2008; Hollander *et al.*, 2010). Would perhaps a prolonged self-administration of apo eventually result in an augmented, uncontrolled intake of the drug? Would the addiction be due to the incidence of an apo-incentive sensitization, or rather to the development of an apo tolerance? Would the posited incentive sensitization or the drug tolerance be context specific? Would the addiction lead to withdrawal symptoms upon cessation of apo administration? All this, no doubt, constitutes a potentially worthwhile research program.

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### Conflicts of interest

There are no conflicts of interest.

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