The effects of apomorphine in pigeons: Some supplementary notes

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Summary. These supplementary notes pertain to the Delius, Acerbo, Krug, Lee, and Leydel (2015) paper and summarize some earlier findings about the influence of the environment on the apomorphine (apo) effect, describe the variability of apo effects, the effects of apo infusion, the individual occurrence of apo insensitivity, its indifference with regard to reward conditioning, the hysteresis due to treatment shifts, an extension to the state discrimination account, the effect of a pecking response restraint, a supplement to the conditioning model, some additional remarks regarding the generality of this model and a possible addition to it, a characterization of the response stereotypy, the difficulties with peck type conversions, the relation displacement activities, the occurrence of individual response idiosyncracies, the "mystery" of apo specificity, and a summary of the pharmacological support for the neural model.

Introduction. The senior author's group work on the effect of apo (apomorphine) on birds began in 1975 after coming across papers by Amsler (1923), Dhawan and Saxena (1960), and Brunelli et al. (1975) on the pecking occasioned by apo administrations in birds. We first carried out a preliminary, unpublished study on preferences of domestic chicks (*Gallus gallus*) injected with 1 mg/kg apo i. m. for varying colors of pecking targets, small dots affixed to the walls and floor of their enclosures. This led to a somewhat more extensive study on apo-elicited pecking in pigeons (*Columba livia*; Basten-Krefft, 1977). It was in the course of this latter study that we noticed the sensitization that occurred with repeated apo injections and began to suspect that it might involve a learning process. This led to a series of papers on the subject: Deviche, 1983; 1985; Delius, 1985; Lindenblatt and Delius, 1987, 1988; Burg et al., 1989; Siemann and Delius, 1992a; Wynne and Delius, 1995, 1996; Godoy and Delius, 1999; Godoy et al. 2000; Keller and Delius, 2001; Delius et al. 2002; Keller et al., 2002; Acerbo et al., 2003a, 2003b; Acerbo and Delius, 2004, Acerbo et al., 2005; Delius et al. 2015. These notes are meant to put on record a number of collateral findings that accrued while carrying out the above research as well as a number of further experiments, some of them of a preliminary nature, that have not been hitherto published. For better comprehension the notes should be read in conjunction with the Delius et al. (2015) paper.

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welfare laws and regulations. The experimental work was all completed before 2006. Where warranted, non-parametric Mann-Whitney U tests were employed to assess the one-tailed significance of between-groups response differences.

Early findings. Our initial domestic chick study indicated that under apo they showed a preference for dots that strongly contrasted in brightness against the white background without any regard for their particular color. A further study using pigeons (Basten Krefft, 1977) yielded a similar result in that there was no color preference that could be correlated with those reported by Delius (1968) and Saghal and Iversen (1975). This might relate to the circumstance that apo promotes a retinal dark adaptation, i.e. the partial onset of color-blind scotopic vision (Delius et al., 2015). More specifically, it was found that dark green dots on a white background and yellow dots on a black background yielded closely similar pecking rates. However, Basten Krefft's study suggested that Bochum stock pigeons underwent a rapid sensitization upon repeated apo treatment, a theme that was specially pursued in the publications listed earlier.

Apo effect variability. Apart from the nature of the pecking targets offered, the main factor affecting the rate of apo-induced pecking in pigeons are both the drug dose administered and the sensitization to apo that the birds have previously undergone (Delius et al., 2015). But factors other than targets, dosage and repetition can modulate the effectiveness of apo. Even though weight-adjusted doses were used in all our studies, we have noticed that with a given per-kg apo dose, lighter pigeons tended to peck somewhat more than heavier pigeons. This is likely to be the case because some fraction of the apo injected absconds into the surplus fat tissue that mostly characterizes the weightier pigeons (Levi, 1977; Gancher, 1995; Neef and van Laar, 1999). Krug and Delius (unpublished data) found that when treated with 0.5 mg/kg apo, a group of 6 pigeons kept-food deprived at 80% of their normal weight, evinced significantly, 15% augmented unconditioned responses (URs) and sensitized responses (SRs) (cf. Brunelli et al., 1975; Bell et al., 1997) even though apo has a marked appetite-suppressing effect in pigeons (Deviche, 1984). However, the sensitization-related incremental responses (IRs) and the conditioned responses (CRs; see Delius et al., 2015) were not enhanced by the food deprivation. Incidentally, thirst also augmented the UR and SR pecking response to apo (Wynne and Delius, 1995) but without apo having a thirst-suppressing effect. We have also noticed that doses of apo are slightly more effective when given during the morning and the later afternoon than those given at mid-day and in the early afternoon. This coincides with the double-peaked diurnal pecking activity cycle commonly exhibited by pigeons (Hörster et al., 2003; cf. Gaytan et al., 1999). The time of the year has similarly been found to have some influence, the response to doses of apo being rather variable during the autumn molt and somewhat reduced in winter than in spring and summer. Stress has been reported to enhance the responsiveness to apo in rodents (Cabib et al., 1988; Cabib and Puglisi-Allegra, 1991) and stress has also been found to induce modifications in dopaminergic transmission mechanisms (Kalivas and Stewart, 1991); indeed, it has been reported that a sensitization to stress transfers to a sensitization to psychostimulant drugs (Robinson et al., 1985). However, the stress produced by extra saline injections intercalated within an apo treatment sequence did not have any peck-enhancing effect in the four pigeons that were tested; it is, however, possible that the stress treatment employed was too mild to be effective (Keller, 2001).

Apomorphine infusion effects. In rats it has been found that a continuous infusion of cocaine, in opposition to intermittent administration, leads to the development of tolerance rather than sensitization (Johansson et al., 1992; King et al., 2004). Under anesthesia (cf. Acerbo & Delius, 2004), pigeons were implanted with 0.2 ml, seven-day intra-peritoneal osmotic pumps (Alzet, Cupertino, California). The pumps of eight birds were filled with an apo solution that

resulted in the infusion of 0.5 mg/kg/day per pigeon. Another eight control pigeons were implanted with saline filled pumps. While the infusion was taking place the pigeons were kept in white-walled, green-dotted experimental cages. Every second day they were video-recorded for 20 min. After the infusions had ended, the pigeons were returned to their home cages. After a two-day break the pigeons were injected once a day with a 0.5 mg/kg apo dose and placed into the experimental cages for 20 min during six consecutive days. Only one of the apo-infused pigeons exhibited somewhat more than control-level pecking towards the end of the infusion period. Upon being injected once a day with 0.5 mg/kg apo, the apo-preinfused pigeons pecked significantly more than the control saline-preinfused pigeons on day 1 (698 ± 157 against 205 ± 150 pecks/20 min, $p < 0.05$, $U(8,8) = 15$) indicating that the infusion had occasioned a comparatively minor sensitization. However, the near-asymptote level reached by the apo-preinfused group was lower than that reached by saline-preinfused group (day 6: 1986 ± 187 against 2950 ± 237 pecks/20 min, $p < 0.01$, $U(8,8) = 9$), an indirect sign that the apo-preinfusion had yielded some tolerance. This apparent contradiction is similar to one that Godoy et al. (2000) observed when pigeons presensitized with 0.2 mg/kg apo daily injections were afterwards switched to a daily 0.5 mg/kg apo dose treatment. They too obtained a somewhat increased response on day 1 of the latter treatment but only a comparatively small subsequent sensitization increment. As to a possible mechanism underlying the development of a tolerance to apo, see the later *Presynaptic inhibition role* section.

Aberrant individuals. Occasional individual pigeons of both Bochum stock (about 1 in 100) and Konstanz stock (about 3 in 100) have been found to peck strikingly little or even not at all in response to apo. However, in the course of two experiments carried out at about the same time using pigeons bred by the Konstanz University Animal Facility, we encountered a cluster of 11 pigeons that pecked very little or not at all in response to apo, while another 21 pigeons tested at the same time responded to the drug normally. This was equivalent to a 34 in 100 insensitive pigeon rate, much higher than the above noted rates.

The facility's breeding program that had started about 12 years previously involved keeping 6 breeding pairs which were periodically renewed. As discovered in retrospect some accidental inbreeding had occurred. Records showed that all the above mentioned unresponsive pigeons stemmed from 5 different breeding pairs; the majority of the pigeons found to be normally responsive stemmed from another 2 breeding pairs, these involving no traceable inbreeding. Three of the above 5 pairs that were parents of 7 of the 11 unresponsive pigeons had an identical pair of grandparents. A fourth pair which had produced 2 of the 11 unresponsive pigeons involved a partner pigeon that had been tested as apo-unresponsive a year before. Nothing specific was known about the pedigree of the fifth pair that produced the remaining 3 unresponsive pigeons. Twenty-one pigeons that were found to be apo-responsive in the same two experiments stemmed either from the 5 breeding pairs just mentioned, or from another 2 breeding pairs which had produced only apo-responsive offspring as far as we knew. The 6 parent pairs for Experiment 3, *Selective parentage* in Delius et al. (2015) were picked from these 35 pigeons. Based on these preliminary findings, it was tentatively hypothesized that we might be dealing with a normally frequent dominant **A** gene and a normally rare recessive **a** gene where the AA and Aa pigeons would be responsive to apo and the aa pigeons would be unresponsive to apo. But the results of Experiment 3 in Delius et al. (2015) did not lend support to such straight-forward accounts.

Rewarded conditioning. It is well established that dopaminergic mechanisms are involved in the mediation of reward in birds and mammals (Delius and Pellander, 1982; Woolverton et al., 1984; Gardner, 1997; Sesack and Grace, 2010; Flagel et al., 2011). It seemed possible that the degree of apo-responsiveness of individual pigeons might be correlated with their reward

(reinforcement) sensitivities. Out of the pool of pigeons tested in Experiment 3 of Delius et al. (2015), Delius, Krug, and Lee (unpublished data) selected 4 particularly apo-unresponsive and 4 particularly apo-responsive birds. They were kept food-deprived at 80% of their normal weight throughout the experiment. Four horizontal conditioning platforms controlled by a personal computer were used (see Experiment 6 in Delius et al. (2015); Xia et al., 1995). The pigeons were first classically-instrumentally conditioned to key-peck (autoshaping; cf. Siemann et al., 1996). The two keys were illuminated with a diamond pattern (5 central diodes lit) for 8 sec at 30 sec intervals. At the end of each stimulus presentation between 5 and 8 millet grains were delivered on one or the other key by an automatic feeder. However, a peck to a key led to an immediate millet reward being delivered on the relevant key, this being followed by the next interval. This first phase ended when at least 32 key-pecks had been issued within a block of 40 trials. In the next, purely instrumental conditioning phase the interval was reduced to 3 sec and the stimulus presentation was increased to 40 sec. Pigeons were now only millet-rewarded when they pecked the stimulus-illuminated key. This phase ended when 32 of the trials within a 40-trial block resulted in 10 or more rewards. The third phase involved a partial reward schedule. The pigeons had to issue 6 repeated pecks to the key before they received a grain reward. This phase ended when again 32 of the trials of a 40-trial block had yielded at least 6 rewards. The fourth phase involved a discrimination learning task. A trial began with the simultaneous presentation of two stimuli, a Z and an H shaped pattern (size: 5 x 5 diodes). The right/left key allocations of the relevant stimuli were randomized across the successive trials. The Z shape was defined as correct, the H shape as incorrect. Three pecks to the correct stimulus yielded a millet reward; three pecks to the incorrect stimulus yielded a 5 sec time-out period. The experiment was terminated when 32 of the trials of a 40 trial-block ended with rewards. The apo-responsive pigeons needed a median 44 (range 27–58) blocks and the apo-unresponsive pigeons needed 41 (range 21–67) blocks to complete the experiment. The two kinds of pigeons were thus indistinguishable in terms of food-conditioned pecking and thus presumably in food-reward sensitivity (cf., however, Coenders et al., 1992). Unfortunately, we have not compared the conditionability of apo-naive and apo-sensitized pigeons in a similar manner.

Incidentally, Glickman and Schiff (1967) have considered why it is reasonable to expect that stimuli which are effective as unconditioned stimuli in classical conditioning should also be effective as reinforcing stimuli in instrumental conditioning. They argued that in the organism's phylogenetic past it would have been inevitable for certain stimuli to innately trigger approach responses and for others to trigger avoidance responses. Subsequently it would have been natural for them to evolve the capability of enforcing that other, originally neutral stimuli which happened to precede them repeatedly, would come to elicit appropriate learned preparatory approach or avoidance responses. That is, the triggering stimuli would have been selected to acquire appetitive or aversive conditioning properties. These appetitive unconditioned stimuli would then have been selected to enforce that originally neutral responses, which happened to precede them repeatedly, became more or less frequent, i.e. the respective stimuli were selected to acquire rewarding or punishing (that is, reinforcing) properties. Even though it is a short-cutting, centrally acting artificial stimulus, apo administration offers itself as an example of a both triggering (i.e. releasing) and (appetitively) reinforcing stimulus.

Condition shift hysteresis. In Experiment 5 of Delius et al. (2015), pigeons first apo-treated in the "weaker" dark condition only attained a lesser near-asymptote pecking level when shifted to the "stronger" light condition than pigeons first apo-treated in this latter light condition. Conversely, pigeons first-apo treated in the "stronger" light condition attained a similar near-asymptote pecking level when shifted to the "weaker" dark condition than

pigeons first apo-treated in the later darker condition. These results are reminiscent of the outcomes of the experiment by Godoy et al. (2000). In that experiment, midway switches between 0.2 and 0.5 mg/kg doses of apo led to an almost-equality of the near-asymptotic levels of pecking elicited by the two different doses. Godoy et al. interpreted their results in terms of a conditioning mechanism responding to a "weak" and a "strong" US_{apo}. However, in view of the outcome of Experiment 5, their results might be better understood in retrospect as consequences of the use of a "weak" and a"strong" CS_{apo}. This dose history dependence (hysteresis, cf. Pleuvry, 2005) of apo sensitization could be of clinical relevance (cf. *Apomorphine infusion effects* above).

State discrimination specificity. Here we add that in Experiment 6 of Delius et al. (2015) we run a further series of daily sessions with the pigeons after 2 mg/kg amphetamine or 4 mg/kg cocaine injections, these replacing the previously used apo administrations. With both these drugs the pigeons chose the two alternative response keys at near 50 % chance level. Whatever states these two drug dosages induced, they were thus dissimilar from the state induced by the 0.25 mg/kg apo doses. Notice though that our pigeons were not specially trained to distinguish the amphetamine and cocaine states from the saline state (cf. Järbe, 1984; Garza and Johnson, 1985).

Pecking response restraint. When discussing the conditioning account of apo sensitization Delius et al. (2015) referred to the role that peck-produced sounds might play as a factor signaling the "under-apo state." Here we report a further result relevant to that issue. Pigeons, which had been previously equipped with a small, tapped metallic block firmly cemented to the cranium while under anesthesia, were sensitized with daily repeated 0.5mg/kg apo doses in the white-walled, green-dotted experimental cages while their heads were fixed to the arm of a stand with the help of a small screw (Mallin and Delius, 1983). When tested afterwards while freely moving in the same cage first under saline and later under apo the four pigeons showed neither pecking IR nor pecking CR (Krug and Delius, unpublished data). It appears that an actual execution of the apo-induced pecks is essential for the development of both the IR and CR to apo. Note that the head-anchoring not only prevented auditory, but also tactile peck-occasioned re-afferences. More generally, it seems that an unrestrained execution of the response elicited by a psychostimulant tends to facilitate the development of sensitization to these drugs (Acerbo and Robinson, unpublished data, amphetamine, locomotion in mice). In conventional Pavlovian conditioning an unhindered execution of URs is almost always found to be necessary for the emergence of CRs (but see Richardson and Hansen, 1980). It may be that sensory re-afferences are essential for conditioning to occur.

Conditioning model supplementation. Delius et al. (2015) argued that the context-specific sensitization of pigeons could be best understood as being the product of a Pavlovian conditioning process in which the cage context and an apo state acted as a conjunctive apo X cage-conditioning stimulus rather than a disjunctive apo **+** cage-conditioning stimulus. It was not specified, however, how the sensitization conditioning proceeded. Here we add that a simple Bush-Mosteller learning operator $\mathbf{\Delta r_n+1 = (a-rn)\bullet\beta}$ which determines the pecking response increment $\mathbf{\Delta r_{n+1}}$ at each new trial **n+1,** where $\mathbf{r_n}$ is the pecking response at the previous **n**th trial, **a** is the empirically estimated final asymptote of pecking response with a given apo dose and **β** is a gain adjustment parameter, was sufficient for a reasonably good simulation of apo sensitization results. Expressed in an algorithmic format it means that the successive total session pecking responses **r** were updated apo X cage session by apo X cage session according to $\mathbf{r \leftarrow r+(a-r)\bullet\beta}$. We found that $\beta \approx 0.4$ parameter values were adequate to model the mean sensitization of Konstanz stock pigeons to 0.5 mg/kg apo doses when the empirical response at first treatment r_1 was taken as the initial response value and when the

empirical asymptote value was set to a = $(r_6+r_7)/2$. A higher $\beta \approx 0.6$ value was found suitable for the simulation of the mean sensitization of Bochum stock pigeons.

Conditioning model generality. Delius et al. (2015) proposed a conditioning account of the apo sensitization of pigeon pecking. But they also considered to what extent it might be applicable to the psychostimulant sensitization of rat locomotion. In that context they referred to the differing environmental adaptations of the two species; here we expand the discussion of one aspect of that issue. Homing stock pigeons normally operate in wide and variable environments while laboratory rats normally operate in a restricted and constant environment. Nevertheless, observations suggest that the former are more novelty-weary than the latter. While untreated laboratory rats, as a rule, begin to explore a novel environment actively within a few minutes of being placed into it, untreated pigeons will usually not begin to do so even after several tens of minutes. Indeed, after showing a prolonged fear-related immobility response they often shift directly into an escape-related, so-called ”pergressive” behavior, without engaging in any interpolated exploratory behavior (Delius, unpublished observations). Apo given to pigeons has a noticeable appeasing effect (Burg et al., 1989) while amphetamine and cocaine, or indeed apo given to rats has a markedly arousing effect (Hooks et al., 1994). Pigeons treated with medium doses of apo tend to show some exploratory behavior almost immediately after having been placed into a novel, distinctive cage and do not show any immobility or pergressive responses. Remarkably, apo-treated pigeons show much the same behavior when placed in their familiar home cage; it is as if such a cage acquires some renewed novelty through the apo administration. In young chickens apo administration has indeed been shown to elicit a special, novelty-signaling vocalization (Lanerolle and Millam, 1980). This effect may be due to the perception-modifying effect that was considered above under *Early findings* (see also Delius et al., 2015). The above factors combined could constitute the reason why the novel-familiar quality of cage environments, i.e. the latent inhibitory effect (cf. Honey et al., 2010), is of negligible significance for the apo responsiveness of homing stock pigeons, whilst it appears to be of major importance in psychostimulant-treated laboratory rats (cf. Carey and Damianopoulos, 2006; but see Matos et al., 2010). By the way, Carrera et al. (2013) describe treatments that, within a conditioning scheme, would qualify as trace-conditioning trials which had reinstatement effects (Domjan, 1997) of an excitatory (high dose of apo) or an inhibitory (very low, autoreceptor-driving dose of apo) nature (cf. Mueller and Stewart, 2000). We note, by the way, that a low, 0.01 mg/kg apo dose was also found to have an inhibitory effect upon the spontaneous pecking of pigeons (cf. Deviche, 1985).

Presynaptic inhibition role? Towards the end of the paper by Delius et al. (2015), we consider the possibility of a gradual development of tolerance to apo. We would like to suggest tentatively that a tolerance to apo could possibly come about through a tardive “sensitization” of the autoreceptor presynaptic inhibition, a type of inibition that appears to operate in many, if not all vertebrate dopaminergic synapses (cf. Harvey and Lacey, 1997; Lovinger, 2010). Such inhibition processes are evident in rodents when low doses of apo depress, rather than augment, the locomotory activity of rats and mice. An analogous inhibition of pecking in pigeons has been reported, see above, but as yet the effect has not been studied in detail. It is worth keeping in mind that presynaptic inhibition is not restricted to low doses of dopamine agonists but also occurs with higher doses, even though it is then masked by the stronger postsynaptic excitatory effect of these doses. Although we do not know of any research on this point, it is conceivable that the dopaminergic postsynaptic inhibition might be subject to a gradual transmission efficacy augmentation upon long-term repeated apo treatments. This could eventually surface as an increased tolerance to the drug, which might lead to a seeking of, and an overdosing with apo, that is, an addiction to the drug.

Apomorphine response stereotypy. Our earlier listed published papers provide ample quantitative descriptions of the pecking response to apo but some qualitative descriptive, ethological data needs to be added. The pecking motions at dots elicited by apo involve head forward movements punctuated by so-called fixation stops, an increasing eye convergence, a partial eye closure, and a beak gaping preparatory to grasping much like those observed during feeding (Siemann and Delius, 1992a, 1992b; Ostheim, 1997; Hörster et al., 2002). Pecks directed at cage grid wires are usually accompanied by grasping and tugging, much as is observed in pigeons feeding off grains stuck to a substrate, such as corns on a maize cob. Loose particles, regardless of whether they are food or grit, are mostly grasped but as a rule, they are not swallowed and dropped again. In fact most of the apo pecking is aimed at items that are not edible. The non-ingestive nature of apo pecking may be due to the strong hunger suppressing side-effect of apo (Deviche, 1984). If, however, the pigeons administered apo are kept very hungry – their weight reduced to 80% of normal – they do actually swallow at least some of the food grains offered (Lindenblatt, 1986) even though most of their apo pecking is still directed at inedible targets. In that respect the apo pecking is similar to the pecking that is involved in searching for food (appetitive pecking) rather than pecking involved in ingesting food (consummatory pecking, Siemann and Delius, 1992b). However, it is strange that although domestic pigeons are predominantly ground feeders, their apo-induced pecking is preferentially directed at cage walls rather than floors. Based upon a more involved argument, Pinkston and Lamb (2012) have similarly concluded that apo-pecking is not closely related to forage pecking.

More generally, the pecking for food in pigeons, rather than being an invariant response unit, i.e. a fixed action pattern (Tinbergen, 1951; Zeiler, 1977), has more recently turned out to be quite a variable and adaptable motor pattern (Siemann and Delius, 1992b; Hörster et al., 2002). Beyond that, pecking is a manipulative response that birds also exhibit in functional contexts other than just foraging: hatching, grooming, fighting, and nesting. Based on observations of domestic fowl chicks, Osuide and Adejoh (1973) suggested that apo-induced pecking might be akin to aggressive pecking. Also apo-treated pigeons will sometimes direct some of their pecks at companion pigeons, if available. However, this pecking is not accompanied by wing-hitting and opponent pursuit typical of normal attacks (Ramirez and Delius, 1978; Haag, 1991); moreover, apo has a strong appeasing effect which seems to inhibit any agonistic behavior (Burg et al., 1989; own observations). It is meanwhile fairly clear that also the allo-feather pecking of domestic fowl – a problem in the industrial husbandry of egg-laying hens – is an obsessive kind of stereotypical behavior (caused by boredom?) not related to aggression, which can in fact be exacerbated by apo administration (Hierden et al., 2005; Kjaer, 2009).

Peck type conversion. The *prima-facie* similarity of apo pecking with appetitive pecking led to an effort to convert apo-induced pecking into food-rewarded key-pecking, similarly considered a variant of appetitive pecking. Four pigeons food-deprived to 80% of their normal weight were injected with 0.5 mg/kg apo and returned to their home cages that were equipped with the conditioning platforms used for Experiment 6 in Delius et al. (2015). The only illumination consisted in the lit diode diamond patterns continuously displayed under both keys of the platforms. Pecks directed at either of the keys caused the delivery of an on-key millet reward. Three pigeons out of four did in fact peck the keys even though they actually ingested only a few of the grains offered as rewards. However, when the daily apo administration ceased after five days, only one pigeon continued to peck the keys. In another attempt we offered 4 pigeons previously injected with apo colored spots displayed on a computer monitor equipped with a touch-screen. The monitor formed one wall of an otherwise

black-walled and only dimly illuminated cage. The pigeons were found to be peculiarly reluctant to peck the stimuli displayed on the monitor. When the monitor was replaced by a black panel with stick-on colored dots and the cage was well illuminated, these dots were pecked by three of the four pigeons. But when we tried to convert this apo-induced, touch-screen-detected pecking into food-rewarded pecking only one pigeon showed the required transition. It appears that the causation mechanisms of apo-induced pecking and food-conditioned pecking are sufficiently different as to hinder any smooth transition. Incidentally, in the dim illumination condition of this experiment the pigeons sometimes pecked rather insistently at the infrared emitting diodes located within the touch-screen frame, indicating that they were somewhat sensitive to this kind of light (cf. Experiment 5, Delius et al., 2015). The same factor may have been responsible for the reluctance to peck the monitor stimuli as it can be expected that in the relative darkness, the pigeons saw their bill being disturbingly lit up when it penetrated the infrared beams.

We also attempted to convert conditioned, food-rewarded key-pecking into apo-induced key-pecking. A pecking of the latter type would much facilitate an automatic recording of apo-elicited pecking. Four pigeons food deprived to 80% of normal weight were trained to peck an illuminated vertical key set into a wall of a cubic white-walled experimental cage for a food reward. They were then gradually accustomed to pecking the key several times before receiving a reward. Eventually the pigeons were being rewarded on average for every 30th peck (range 5th to 100th), i.e. a lean variable ratio schedule ensuring a high and continuous rate of pecking throughout the daily one-hour sessions. Then the pigeons were administered doses of apo increasing from 0.1 to 1 mg/kg over successive sessions. The initial lower doses of apo slightly augmented the key-pecking rates. However, all four pigeons began to disregard the grain rewards and ceased to peck the key when 0.5 mg/kg or higher doses of apo were administered, switching instead to pecking alternative non-key targets (Vollmar and Delius, unpublished data). An analogous finding was reported by Abelson and Woods (1980), but Graeff and Oliveira (1975; see also Pinkstone and Lamb, 2012) succeeded in increasing the rate of food-rewarded key-pecking with apo doses of up to 1 mg/kg in some of their pigeons.

Displacement responses. Behavioral stereotypes have been described as occurring in animals, and indeed humans, in response to brief stressful events such as motivational frustration or motivational conflict, and in response to protracted stressful conditions such as persistent pain or prolonged constraint. Examples of the former, referred to as displacement activities, are the occurrence of preening motions in the context of sexual encounters in ducks or ground pecking in the context of agonistic encounters in chickens (Delius, 1970; Feekes, 1972; Holland, 1976). Examples of the latter are the occurrence of cleaning obsessions of prison cell inmates, of repetitive fixed path ambulation in bears in zoo enclosures, or indeed the compulsive pecking (and tugging) shown by long-term caged pigeons (Palya and Zacny, 1980; Ödberg, 1989; Mason, 1991; own observations). Repetitive motor stereotypes also occur as symptoms of mental illness such as head-banging in autistic children or exaggerated hair combing in psychotic patients (Frith and Done, 1990; Ridley, 1994). Randrup and Munkvard (1967) were the first to suggest that stereotypes observed after administration of amphetamine to animals and humans might serve as model for stereotype responses seen in psychiatric patients. That behavior stereotypes can arise upon activation of dopaminergic mechanisms has continued to receive support (Robbins et al., 1990; Willemse and Spruijt, 1995; Chartoff et al., 2001; Berridge et al., 2005). However, it is fair to draw attention to the fact that drug varieties and dosages interact with species and even stock differences regarding the types of behavior stereotypes elicited by dopaminergic drugs. Among fish, amphibian, reptile, and bird species the repetitive responses reported in response to apo have been snapping, chewing, pecking, scratching and preening (e.g. Nymark, 1972; Andersen et al., 1975; Nistico and Stephenson,

1979; Machlis, 1980; Glagow and Ewert, 1997). Among rodent species and strains the stereotypies variously involved grooming, yawning, sniffing, gnawing, biting, climbing, and ambulation (e.g., Fekete et al., 1970; Ljungberg and Ungerstedt, 1977; Kendler and Davis, 1984; Cools, 1994). In humans, smaller doses of apo have been reported to elicit repetitive chewing and yawning (Szechtman et al., 1987; Lal, 1988; Casas et al., 1995).

Response idiosyncrasies. Beyond the stereotypy stressed thus far, the pecking induced by apo is characterized by individual idiosyncrasies. Even though most pigeons in Experiment 1 in Delius et al. (2015) pecked at the dots on the side and back walls of the experimental cages right from the beginning, three of seven pigeons receiving the 1 mg/kg apo dose pecked their front wire-grid walls. Two of 16 pigeons receiving 0.5 mg/kg apo and 2 of the 7 pigeons receiving the 1 mg/kg dose pecked the grid cage floor. One pigeon receiving 0.2 mg/kg apo pecked predominantly at its toes. However, such idiosyncrasies go even further. One of the two floor-pecking, 0.5 mg/kg apo pigeons pecked just in front of its feet while staying essentially stationary, whereas the other pigeon pecked with its neck stretched and curved to its left while slowly turning from peck to peck in the same left direction. Of the 14 wall-pecking, 0.5 mg/kg dose birds, one pigeon, for example, pecked an indistinctive point high up on the back wall of the cage without any ambulation. Another pigeon pecked a particular welding spot in one of the cage corners while occasionally pausing to turning right before returning to peck the same spot. By and large the individual idiosyncrasies were quite stable but, for example, while three of the above pigeons retained much the same style of pecking throughout the six sessions, the pigeon mentioned last stopped turning from the fourth session onwards (see remarks about response stability below). As to the turning, it varied between individuals from 0 full turns/20 min to an exceptional 19 full turns in one – in this case right – direction/20 min, with a median 4.5 turns/20 min, in a sample of 12 Konstanz stock 0.5 mg/kg apo-sensitized pigeons during their 6th daily treatment. Eight pigeons turned 2 or more full turns/20 min, of which 3 turned right fairly consistently and 4 turned left pretty consistently while the remaining pigeon turned as much right as left. Additional more casual observations indicated that there was no population consistent-turning handedness even though an individually consistent handedness has been shown to be reasonably common in pigeons (Güntürkün et al., 1988).

It would be worth examining whether selective breeding might not have differentiated idiosyncrasies further. However, no salient differences in idiosyncrasies were noticed between Bochum and Konstanz stocks during Experiment 2 of Delius et al. (2015). During Experiment 3, the apo-unresponsive pigeons were observed to preen rather than to peck but this might have simply been the case because the same dose of apo was a low dose for them while it was a high dose for apo-responsive pigeons (see below).

Part of the response idiosyncrasies that were observed during Experiment 1 can be ascribed to apo dose differences. The 0.2 and 0.3 mg/kg apo administrations elicited many so-called peck intentions or air-pecking, consisting of head forward and eye convergence motions without leading to actual substrate contacts. Goodman (1981) incidentally, observed that apo administration could also promote the occurrence of mandibulation (repetitive small amplitude yaw movements) and swallowing (presumably of saliva) movements, two further pecking-related responses. Over and above these findings, 2 of our 8 pigeons receiving 0.2 mg/kg and 4 of the six pigeons receiving 0.1 mg/kg apo showed plumage pecking, which often merged into preening responses involving a drawing of the feathers through the beak. The peck intentions and plumage preening shown by the pigeons administered 0.2 mg/kg apo, however, was mostly replaced by regular pecking as the sensitization to the drug set in with repeated treatments. A notable preening response was also observed when the effect of a 0.5 mg/kg apo

dose was inhibited by the co-administration of the dopamine antagonist haloperidol or SCH-23390 (Acerbo et al., 2003; Acerbo and Delius, 2004). Foot kicks are another, though infrequent response to apo; these are leg-flicking movements by which pigeons normally shake off items sticking to their feet (cf. limb flicking in cats: Trulson and Crisp, 1982). Increased yawning, headshaking, and limb-stretching have been recorded as accompanying apo-induced preening (Deviche, 1985; Delius, 1988; Lindenblatt and Delius, 1988). Compared with pecking, these grooming and comfort activities are infrequently observed. In an experiment aimed at augmenting plumage pecking, 0.5 mg/kg apo-treated pigeons were placed in plain white-walled cages but had a red wool thread 3 cm long tied to a right-wing (4 pigeons) or to a left-wing feather shaft (4 pigeons). This resulted in a marked preferential pecking of the threaded wing on the third treatment day. A test on the fourth day in which no thread was attached resulted in very little wing-pecking – no wing preference being shown – but in much wall-pecking instead (Keller, 2001).

Locomotion, the dominant response when apo is administered to rodents, is not a salient part of the apo response in pigeons. Though probably weakly present, an ambulation response appears to be suppressed by a competing tendency to repeatedly peck a particular localized target. Nevertheless, some slow walking around the cage occasionally precedes and sometimes accompanies the pecking caused by medium doses of apo. It has been suggested that we might not have observed locomotor activity as an apo-induced response in pigeons because such activity was constrained by the small cages used. Indeed Maclean (1990, p. 336) has reported that apo-treated free ranging turkeys would show "incessant running." On rarer occasions we have observed episodes of on-the-spot stepping in apo-treated pigeons which could be interpreted as a variant form of foot kicking, see above, or indeed, as an inhibited form of walking. Flying was of course not possible in our experimental cages. However, we never observed any wing-unfolding in response to apo, a preparatory flight maneuver that pigeons often show in these cages when frightened. A few trials with 1 mg/kg apo treated pigeons in a larger aviary-type cage did not reveal any augmented locomotion but plenty of localized pecking activity.

By and large the response idiosyncrasies shown by individual pigeons tend to be retained across many apo treatment repetitions and across week-long intervals. Experiment 5 of Delius et al. (2015) nevertheless revealed that a switching of pecking style would occur with a change in stimulus condition. In that experiment the videotape-recorded pecks were initially counted and sub-classified as wall, floor, or body pecks. The floor pecking included some toe pecking, but the camera's perspective mostly did not allow a secure distinction between these two response variants. Most of the pigeons showed wall pecking in the light situation but exhibited floor, or more rarely, body pecking in the dark condition. The strong predominance of floor and body pecking in the dark condition undoubtedly represented an adjustment to the peculiar sensory situation. Congruent findings have been reported by Pinkston et al. (2008).

In the more normally used light condition, about 80% of the pigeons chose to peck the cage walls. Lindenblatt (1986) nevertheless observed that a group of eight pigeons being treated with 1 mg/kg apo in a well-lit plain wire-grid walled and grid-floored cage for the first time, all pecked the wire-grid floor. When placed in dotted wall cages for their second apo administration they persisted with floor pecking. Nevertheless, most of the pigeons eventually switched to wall pecking as they were repeatedly treated in the dotted wall cages. In an attempt to obtain more persistent floor pecking, we tried cages with a multicolored grit floor-litter: when placed untreated into these cages 3 out of 4 pigeons exhibited some spontaneous floor pecking. Upon being treated with 0.5 mg/kg apo all 4 pigeons began with floor pecking but as the sensitization began to take effect, only one of the pigeons persisted with this type of

response, the others switching again to the more usual wall-pecking. Another group of four pigeons kept at 90% of their normal bodyweight, and thus mildly hungry, were pre-trained to search for grains mixed into the floor grit. All four pigeons naturally became avid floor-peckers. But even so, when they were repeatedly treated with 0.5 mg/kg apo, only two continued to floor-peck (Krug, Lee, and Delius, unpublished data).

Efforts were also directed at binding the predominant apo wall pecking to a particular location by furnishing either only the left (four pigeons) or only the right (four pigeons) white walls of experimental cages with green dots. This resulted in a clear-cut preference for the dotted wall side by the third daily 0.5 mg/kg apo application but when tested on the fourth day in all white-walled cages there was no significant preference for the previously dotted cage side. It is the case, though, that Keller and Delius (2001) sensitized pigeons to apo either in a white-walled, green-dotted cage or in a black-walled, yellow-dotted cage and control-exposed them to the alternative cages under saline. When subsequently tested in a checkerboard white-green and black-yellow wall-lined cage they exhibited a very strong preference for the checkerboard fields that corresponded to the wall lining they had experienced during the apo sensitization treatment. However, beyond this latter result we have not been successful in achieving an experimentally controlled fixation upon particular pecking targets.

Apomorphine specificity. There is the possibility that at least some of the response and target variations reported above might arise through the activation of different dopamine receptors. Dopamine receptors that promote the synthesis of cyclic adenosine monophosphate (cAMP) are grouped into a D1-like family (D1, D5), while those that inhibit cAMP synthesis are grouped into a D2-like family (D2, D3, and D4; Kebabian and Calne, 1979; Sealfon and Olanow, 2000). Apo is recognized to be a dopamine agonist that binds nearly equally well to both D1- and D2-type receptors. Studies involving the co-administration of receptor-type-specific antagonists together with apo have suggested that the apo-induced pecking of birds is primarily the result of an activation of D2-type receptors, but is much potentiated by a simultaneous co-activation of D1 receptors (Osuide and Adejoh, 1973; Zarrindast et al. 1992; Dehpour et al., 1995; see also Dose and Zolman, 1994). Regarding the elicitation of stereotypies in rodents, both D1 and D2 receptor activations have been implicated in the past (Germeyer et al., 2002); more recently the importance of D1-type receptor stimulation has been particularly stressed (Chartoff et al., 2001; Berridge et al., 2005; Dias et al., 2010).

Acerbo et al. (2003) found that the co-administration of haloperidol (hal), a strong antagonist of D2-type receptors and a weaker antagonist of D1-type receptors, has a pronounced suppressive effect on apo-induced pecking in pigeons. However, Acerbo and Delius (2004) have also found that an intra-cerebral co-administration of SCH-23390, a specific antagonist of D1-type receptors, is capable of inhibiting apo-induced pecking. The dopamine agonists bromocryptine, quinpirole, and SKF-38393 have also been tested. Various doses of these drugs – those reported effective in rodent studies – were tested three times in ascending order in three groups of 4 pigeons each. With bromocriptine (Tocris-Cookson, Bristol, England), a D2 agonist, it was found that compared to a control saline treatment, a 4 mg/kg dose elicited some preening but no pecking, an 8 mg/kg dose yielded some preening, some pecking, and some ambulation, a 16 mg/kg dose elicited a bout of around 300 pecks/30 min, no preening, and little walking, and finally, a 20 mg/kg dose yielded very little pecking, no preening, and no locomotion. With quinpirole hydrochloride (Sigma-Aldrich, Munich), a D2 agonist, it was found that both 0.1 and 0.2 mg/kg doses elicited around 50 pecks/30 min, as well as some ambulation whereas the higher doses of 0.4 and 0.8 mg suppressed virtually all motor activity. With D1 agonist SKF-38393 (Research Biochemicals, Natrick, Massachussets), it was found that a 2 mg/kg dose elicited some preening and no pecking, a 4 mg/kg dose yielded some

preening and some pecking, a 6 mg/kg dose elicited more pecking – around 300 pecks/30 min – and little preening and finally a 8 mg/kg dose elicited marked ambulation, some preening, and very little pecking. Eight different combination doses of bromocriptine or quinpirole (both D2 agonists) and SKF-38393 (D1 agonist) were tested on another eight pigeons, four of which had been presensitized to apo. The various combinations were each tested at least three times in four of the pigeons. The combinations of 16 mg/kg bromocriptine plus 2 mg/kg SKF-38393 and 0.2 mg/kg quinpirole plus 4 mg/kg SKF-38393 proved to be the two most effective mixtures for producing pecking. But the pecking elicited by these combinations – about 300 and 150 pecks/30 min, respectively – did not exceed that produced by the most effective doses of either bromocriptine alone or SKF-38393 alone (see above). In any case, the effect of the agonists, whether alone or combined, was much smaller than that of the maximally effective dose of 1 mg/kg apo, which yielded some 1000 pecks/20 min, or even of the routinely employed standard dose of 0.5 mg/kg, which produced some 500 pecks/20 min upon first application. No detectable differences were found between the responses of apo-presensitized and non-presensitized pigeons to the agonist mixtures; that is, the sensitization to apo did not seem to transfer to the agonist treatments. Moreover, repeated once-daily injections of the most effective agonist mixture over 5 days led to a decrease of the pecking response, suggesting the development of tolerance rather than sensitization.

Chronic administration of the dopamine antagonist haloperidol (hal) in rodents results in a persistent hypersensitivity to dopaminergic drugs (cf. Geurts et al., 1999; Quieroz et al., 2002). We thus examined whether continuous infusions of hal in pigeons would lead to a corresponding effect. Eleven pigeons were implanted with 0.2 ml, seven-day intra-peritoneal osmotic pumps (cf. *Apomorphine infusion effects* above) filled with a solution that yielded an infusion of about 0.20 mg/kg/day hal per pigeon. Eight control pigeons were implanted with saline-filled pumps. The pigeons were kept in white-walled, green-dotted experimental cages. Every second day they were video-taped for 20 min. The hal infusion had a noticeable sedating effect on all pigeons from about the 3rd day onward (cf. Clinton et al., 1987). Afterwards the pigeons were returned to their standard home cages; all detectable signs of sedation vanished by the second day. After two further days, all the pigeons were injected once a day with a 0.5 mg/kg apo dose and placed into the experimental cages for 20 min over six consecutive days. One hal-infused pigeon was excluded because it was almost totally unresponsive to apo. On day 1 there was no difference in pecking between the hal- and saline-infused group (196 ± 81 versus 205 ± 150 pecks/20 min). The near-asymptote pecking on day 6 by the hal group was significantly less than the pecking shown by the control group (2170 ± 223 against 2950 ± 337 pecks/20 min, $U(10,8) = 13$, $p < 0.01$). It is evident that the hal preinfusion did not lead to the expected cross-sensitization to apo. This finding could be due to the fact that the dopamine antagonist hal has a half-life of roughly one week in live mammalian tissue (Cohen et al., 1992; Kornhuber et al., 1999) and that the break between the hal treatment and the apo challenge was too short to ensure a sufficient clearance of the apo-antagonist. It is also possible that a larger dose of hal may be needed to generate a cross-sensitization. However, using four pigeons, Delius and Lee (unpublished data) found that daily 0.5 mg/kg hal injections for ten days similarly had no cross-sensitization effect on a subsequent 0.5 mg/kg apo sensitization course (cf. Mattingly and Rowlett, 1989).

Attempts were made to induce pecking by augmenting the synthesis of endogenous dopamine through the administration of precursor L-DOPA (cf. Cheng et al., 1975). Four pigeons were injected intraperitoneally with 200 mg/kg L-DOPA (Sigma-Aldrich, Munich) on 7 consecutive days. However, their pecking activity on days 6 and 7 did not differ from that of 4 control saline-injected pigeons. Also, the response of the L-DOPA pretreated pigeons to 0.5 mg/kg apo doses administered after a two-day treatment break was not different from that shown by

the saline pretreated pigeons (Krug and Delius, unpublished data).

In rodents, amphetamine and cocaine, indirect dopamine agonists, yield pronounced bouts of locomotor hyperactivity, much as does apo. Furthermore, when administered repeatedly, all three substances lead to similar sensitization effects (Mattingly and Gotsick, 1989; Zavala et al., 2000; Crombag et al., 2001; Carrera et al., 2011). We thus examined what behavioral effects amphetamine and cocaine would have on pigeons. Two groups of four pigeons each were intramuscularly injected with daily doses of between 0.5 and 8 mg/kg of amphetamine sulfate (Sigma-Aldrich, Munich) or of cocaine hydrochloride (Sigma-Aldrich, Munich) in ascending order and observed for 30 min. The dose-range used was derived from those found effective in various rodent studies. None of the amphetamine doses led to any detectable effects in the pigeons. Specifically, they did not elicit any more pecking than control saline injections. However Goodman (1981; see also Cheng et al., 1975) found that amphetamine doses of above 5 mg/kg and up to 30 mg/kg elicited an increasing pecking response; nevertheless, Idemudia and McMillan (1984), while reporting locomotor behavior as a response to amphetamine, also mention the occurrence of some pecking. The 0.5 mg/kg cocaine dose had no detectable effect in our trials, but doses of 1 and 2 mg/kg elicited noticeable bouts of locomotion compared to control saline injections. The 4 mg/kg cocaine dose yielded little locomotion but elicited repeated retching. Pecking did not occur with any of the cocaine doses (Krug and Delius, unpublished data). These findings contrast somewhat with several reports indicating that both amphetamine and cocaine administrations tend to increase the conditioned, food-rewarded key-pecking of pigeons (Graeff and Olivera, 1975; Schaal et al., 1995; Walker and Branch, 1998) but agree with the fact that both in quail and pigeons, cocaine elicits locomotion but does not yield pecking (Levens and Akins, 2001, Pinkston and Branch, 2010).

The fact is that we do not understand why apo is so outstanding in eliciting pecking of birds when other dopamine agonists are at best only weakly effective. This efficacy, by the way, cannot be ascribed to a possible opioid side-effect of apo, a morphine derivative, since neither opioid antagonist nor opioid agonist administrations have any influence on apo pecking (Deviche, 1985). In rodents apo, although also an otherwise potent dopamine agonist, does not seem to have comparable extra power for eliciting stereotypies (Waddington and Daly, 1993; Baldessarini et al., 1994; Hooks et al., 1994). However, apo has more recently been found to have an indirect agonistic serotoninergic effect in rodents (cf. Mendlin et al., 1998; Carey et al., 2005). This side-effect may actually play a role in avian apo-elicited pecking (Flisikowski et al., 2009; Wysocki et al., 2013). The serotoninergic action of apo might explain why it has a strong hunger-suppressing effect in pigeons (Deviche, 1984; cf. Güntürkün et al., 1989).

Neural model. In the *Discussion* section of Delius et al. (2015), we presented a neural model that accounts for apo sensitization in pigeons. Here we add that the results of studies on pigeons looking into the effects of dopaminergic and glutamatergic transmission blockers on the development of apo-sensitization-related IR and CR generally support the proposed neural model. Concerning a D1 and D2 antagonist it was found that concurrent haloperidol (hal) administration attenuated the US_{apo}-UR pecking link and consequently blocked the development of both the IR and the CR (Acerbo et al., 2003). However, once the IR had been normally acquired, hal did not immediately block its retention. Similarly, once the CR was acquired, hal did not block its retrieval. Once already developed, both these responses thus appear to be no longer dependent on processes mediated by D2-type receptors**.** Concerning a D1 antagonist it was found that concurrent intrastriatal SCH-23390 administration also attenuated the US_{apo}-UR pecking link (Acerbo and Delius, 2004; cf. Dias et al., 2010) and thus also blocked the development of both the IR and the CR. However, once the IR had been

normally acquired, SCH-23390 did not immediately block its retention. Similarly, once the CR was acquired, SCH-23390 did not completely block its retrieval. Inasmuch as neither the D1 nor the D1/D2 type antagonists fully blocked the retrieval of the IR and the CR we presume that the sensitization to apo is not primarily based on modifications of dopaminergic transmission efficacy. The co-administration of Glu-NMDA receptor antagonist dizocilpine (diz) blocked both the development of the IR and the later expression of a CR (Acerbo et al., 2004; see also Zarrindast et al., 2003). But we also found that the retrieval of the CR elicited by the environmental context was similarly inhibited by dizocilpine blockades. This finding does not agree with the standard long-term potentiation (LTP) based model of conditioning which assumes that the elicitation of previously established CRs is not dependent on an activation of NMDA receptors but rather on the activation of Glu-AMPA receptors (cf. Sutton et al., 2003; Wolf and Ferrario, 2010). However, it is a frequent empirical finding that NMDA antagonists nevertheless interfere with the CR retrieval (Battisti et al., 2000; Gargiulo et al., 2005). The overall results agree with the hypothesis that sensitization to apo in pigeons is based on a process leading to an alteration of glutamatergic transmission mechanisms and not primarily an alteration of dopaminergic transmission (Acerbo et al., 2005; see also Hooks et al., 1994).

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