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Specific effects by the psychotomimetic drugs *d*-amphetamine and phencyclidine on the performance of an aversely motivated successive visual discrimination in the rat

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Summary. Rats were trained to perform a conditioned avoidance response to white noise in a conventional two-compartment "shuttle-box". The partition between the compartments had two openings, however, and the correct passage (left *or* right) was signalled by changes in background illumination. In this situation the psychotomimetic compounds *d*-amphetamine (4 mg kg^{-1} IP) and phencyclidine (PCP) (2 mg kg^{-1} SC) were found to selectively disrupt the visual discrimination. The *d*-amphetamine-induced abnormal behavior in this situation has previously been linked to excessive dopamine (DA) receptor stimulation, not controlled by nerve impulse flow and its regulation by important local feed-back mechanisms. Thus, the psychotomimetic effects produced by this compound should not only by due to increased DA receptor activation *per se*, but also to a disruption of normal patterns of firing and release in dopaminergic neurons. There is evidence to suggest that PCP via an excitatory amino acid (EAA) receptor produces a similar net effect on brain meso-limbic dopaminergic neurotransmission via an increased rate of firing, accompanied by regularization of firing (loss of burst activity). In support for a mediation of PCP-induced effects via EAA receptors, the local application of kynurenic acid into the ventral forebrain (4.7 μg, bilaterally) was found also to produce a selective disruption of discriminative performance. It should be noted, however, that *d*-amphetamine-induced loss of discriminative behavior, but not that induced by PCP, was antagonized by haloperidol (0.1–0.2 mg kg^{-1} IP) administration. It is thus possible that at least some effects of PCP in this situation are mediated on the efferent side of the dopaminergic neuron. It is suggested that the abnormal behavior, as evidenced by a loss of discriminative (but not avoidance) behavior, is due to disruption of normal, feed-back regulated, nerve impulse flow.

Keywords: Amino acids – Conditioned avoidance – Discrimination – Nerve impulses – Dopamine – Excitatory amino acids – Amphetamine – Phencyclidine (Rat)

Important of nerve-impulse induced dopamine release for the maintenance of normal behavior

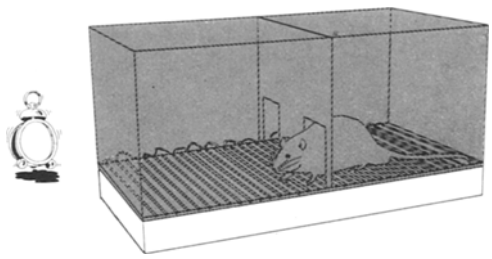
The behavioral activation produced a by direct stimulation of brain dopamine (DA) receptors, beyond presynaptic regulatory mechanisms, can be distinguished as abnormal in comparison with the normal behavior produced by indirect, nerve-impulse controlled, stimulation of the DA receptor, in mice or rats. This distinction could be of importance for drug treatment strategies in neurodegenerative disorders, where the normal presynaptic modulation is missing, but could also be of importance for understanding drug therapies in relation to the pathogenesis of psychotic behavior like schizophrenia, as further discussed in this paper. The restoration of normal behavior by *L*-DOPA administration in animals treated with α-methyl-*p*-tyrosine (α-MT), but not reserpine, serves well to illustrate the principle functional differences between these two modes of DA receptor activation. The separate mechanisms for brain DA depletion by reserpine and α-MT provides the bases for the illustration, since only reserpine interferes directly with storage granules which are of immediate importance for normal catecholamine release by the nerve impulse flow. In fact, it appears that normal granular function not only is important for physiological release mechanisms, but also that an extragranular accumulation of the neurotransmitter may inhibit release [32, 42, 44]. Thus, reserpine blocks the energy-dependent active granular uptake of DA [see 13], whereas α-MT inhibits DA synthesis at the rate-limiting tyrosine hydroxylase step [see 33], leaving granular functions intact. Consequently, it is possible to "refill" α-MT-, but not reserpine-, depleted DA granules by treatment with the DA precursor *L*-DOPA (which bypasses synthesis inhibition at the tyrosine hydroxylase step) [16, 17]. It should be noted, however, that with increasing doses, the DA formed from *L*-DOPA in reserpine-treated animals will eventually diffuse out of the neuron. This "pharmacological release" is presumably beyond control by the nerve impulse flow.

Such a "pharmacological release" of DA will antagonize certain aspects of reserpine-induced behavioral effects, like the suppression of motor activity and of conditioned avoidance behavior [see 9]. A closer examination of the behavioral activation produced by the administration of *L*-DOPA in high doses (or direct acting DA agonists like apomorphine) in reserpine-treated animals, however, demonstrate clear deficiencies in the behavior thus obtained. For example, the normal pattern of habituation to a novel environment is absent [4], operant behavior in a Skinner-box is abolished [3] and when conditioned avoidance behavior is made dependent upon a spatial or a visual discrimination, normal performance is lost [1, 2]. This in contrast to the restoration of normal behavior in these situations by the administration of *L*-DOPA, in low doses, to α-MT-pretreated animals. In the latter situation, the animals thus are asked not only to react to the conditioned stimulus (white noise), but also to make a visual discrimination, in order to avoid the unconditioned stimulus (foot-shock). This

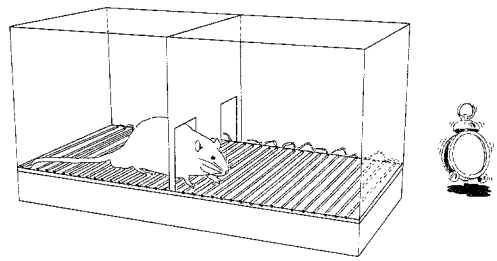
situation has proved particularly useful for the purpose of studying the quality of drug-induced behavioral changes and was used in the experiments presented in this paper. A description of the apparatus, and the testing procedures follows below.

Methodological considerations

The basic equipment in the present studies, was a standard shuttle-box (534 × 255 × 225 mm) for observing conditioned avoidance behavior in rats. For the present purpose, however, the partition dividing the box into two compartments had two openings (77 × 77 mm), rather than just one passage. Thus, as shown in Fig. 1, the rat had the option of taking a left or right turn when moving from one compartment into the other. The experimental chamber, as shown in the figure, was housed in a sound-attenuating, ventilated, enclosure. Dim background light was provided by a 15W discharge lamp and the rat could be observed through a one-way mirror in the front wall.



white noise + dim background = GO LEFT



white noise + bright background = GO RIGHT

Fig. 1. Schematic presentation of the conditioned avoidance apparatus, and the stimulus conditions signalling the right or the left passage for a correct avoidance (or escape) response. Please note the symmetrical ("shuttle-box") arrangement, which means that the rules for correct avoidance (or escape) responding, applies equally from either compartment of the box

At random time intervals, the conditioned stimulus (CS) (white noise, 80 dBA) was presented and, in order to avoid the unconditioned stimulus (UCS)

(intermittent mild electric foot-shock at 0.2 mA), the rat had to cross to the opposite, safe, compartment. The CS was presented alone for a maximal time of 10s and, if no response had occurred within this time interval, followed by CS + UCS, until the rat responded. In addition to this, the rat had to perform a visual discrimination, as described below.

The normal background illumination was approximately 400 lux at floor level. If the CS (or CS + UCS) was presented at this level of illumination, passage through the left opening was required for a correct avoidance (response to CS) or correct escape (response to CS + UCS) (Fig. 1, top). If CS was presented at increased background illumination, a passage through the right opening was required (Fig. 1, bottom). The background illumination was increased by switching on two 75W bulbs, symmetrically placed above the experimental chamber, producing approx. 1,900 lux at floor level.

As mentioned above, the CS was presented at random intervals. The rules for the inter-trial intervals, however, differed between training and testing sessions. Furthermore, during training and pretest, CS or CS + UCS was not terminated until a correct response was performed. In test sessions, CS or CS + UCS was terminated immediately upon the first response and one of the following variables was recorded: [*A*] Correct or [*B*] incorrect avoidance; [*C*] Correct or [*D*] incorrect escape. In addition, the number of inter-trial crosses were registered. For further details see Ahlenius [2].

In the title of this paper, the visual discrimination was designated as "successive". In a successive discrimination procedure, the stimuli to be discriminated (*e.g.* degree of illumination, as in the present series of experiments) are given successively and are thus not present at the same time. This in contrast to a "simultaneous" discrimination, where they would be presented together. As an example, in one version of the box presented in Fig. 1, two lamps were mounted in the partition, visible from both sides, directly above the respective passage. In a simultaneous discrimination procedure, the rat would be asked to pass through the lit (or dim) passage, presented in a random fashion. In our hands, these two procedures are difficult (or perhaps awkward to the rat) and are normally acquired to perfection (90–100 per cent correct avoidance) over a period of 7–10 days. This in contrast to a spatial discrimination (right *or* left passage always the correct alternative) or a conventional shuttle-box avoidance conditioning through one single opening in the partition. These latter procedures are considerably easier (or more natural to the rat) than the successive or simultaneous procedures described above and are normally mastered within 3–4 days. It should be noted, however, that once learned, there is no difference between these various procedures in the retention or stability of the performance under normal, non-experimental, conditions. In fact, once acquired, the successive discrimination avoidance performance may be more resistant to drug treatments than the ordinary two-way avoidance conditioning, in all probability due to a certain degree of over-training in the former situation (unpublished observations). For further details on general procedures of avoidance and discrimination learning in rats (as well as in other animal species) see Sutherland and Mackintosh [43].

Effect of *d*-amphetamine

In low doses, *d*-amphetamine is a well-known psychomotor stimulant in man [see 21], whereas higher doses, particularly after repeated dosing, may produce the symptoms of acute schizophrenia [38]. The centrally mediated stimulant effects by *d*-amphetamine were early demonstrated in a great number of laboratory studies [see *e.g.* 40]. Studies on its mechanisms of action have shown a facilitation of the nerve-impulse induced release of catecholamines, in contrast to the displacement mechanism of tyramine, independent of nerve impulse flow [29, 34, 35, 45]. With increasing doses, however, there also appears to be tyramine-like displacement of central catecholamines [27]. It is important to note that this difference not necessarily shows up in the dose-dependent increase by *d*-amphetamine on DA release, as for example demonstrated by microdialysis [46]. The laboratory studies on the mechanism of action of *d*-amphetamine have been strongly motivated by the clinical observations mentioned above, and the findings of an enhanced dopaminergic neurotransmission provided one of the cornerstones in the dopamine hypothesis of schizophrenia [see 14].

By use of the visual discrimination described in this paper, it was possible to demonstrate qualitative differences in the behavioral stimulation induced by the administration of a "low" (2 mg kg^{-1}), as compared to a "high" (4 mg kg^{-1}), dose of *d*-amphetamine to rats, differences that may be related to the two mechanisms of action by which *d*-amphetamine activates brain DA receptors. As expected, both these doses produced an increased number of inter-trial crosses and the avoidance behavior was unaffected. However, at the high, but not the low, dose the animals performed at chance level on the visual discrimination [6]. Thus, there is evidence for two behavioral mechanisms being affected differently, the graded increase in psychomotor stimulation, as indicated by the increase in number of inter-trial crosses, and an abrupt disruption of the discriminative performance. Interestingly, the *d*-amphetamine-induced abnormal behavior can be normalized by treatment with the DA receptor blocking antipsychotic agent haloperidol (Fig. 2). Haloperidol by itself does not affect the visual discrimination at doses which effectively antagonized the *d*-amphetamine-induced disruption of the discriminative behavior [7, 8]. This observation in fact provides the basis for an interesting double dissociation of drug effects by this procedure. Excessive stimulation of central DA receptors, beyond modulation by the nerve-impulse flow, as produced for instance by high doses of *L*-DOPA or by apomorphine [see 5 and above] and possibly also by high doses of *d*-amphetamine, disrupts discriminative performance, but does not affect avoidance behavior. Dopamine-receptor blocking antipsychotics, like haloperidol or pimozide, on the other hand, suppress avoidance performance without affecting the discriminative behavior. This is illustrated in Table 1 by showing schematically the effects obtained by increasing doses of *L*-DOPA in animals depleted on brain catecholamines by means of α-MT pretreatment [2].

An important aspect of the present model is that it offers a way to study an abnormal behavior induced by *d*-amphetamine at doses where stereotypies have not yet appeared. Furthermore, the disruption of discriminative performance may be considered a *positive symptom* of *d*-amphetamine-induced abnormal

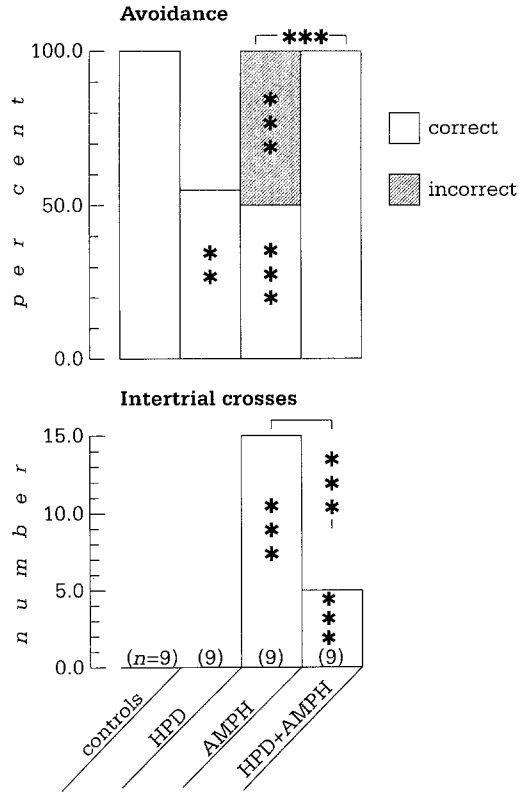


Fig. 2. Antagonism by haloperidol administration of *d*-amphetamine-induced disruption of a successive visual discrimination in the rat. *d*-Amphetamine (4 mg kg^{-1} IP) and haloperidol (0.125 mg kg^{-1} IP) were administered 40 and 20 min before the observation, respectively. The results are presented as medians, based on the performance of 9 rats. The animals served as their own controls using a change-over design [see 28]. Statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test [see 41] for comparisons with the vehicle control condition, or as indicated by brackets in the figure. ** $p < 0.025$, *** $p < 0.01$

animal behavior. This in contrast to the stereotyped gnawing seen at higher doses, a behavior which is but little affected by external stimuli and by its focus on one behavioral activity, at the expense of others, can be regarded as predominantly accompanied by *negative symptoms*. It is also interesting to note that stereotypies, as part of catatonic symptoms in schizophrenia, sometimes are considered more as negative than as positive symptoms [*e.g.* 10, 39]. Needless to say, positive symptoms in the present context do not necessarily imply a correspondence to such symptoms of schizophrenia, but rather that the distinction between positive and negative symptoms in general may prove as useful in the laboratory setting as in the clinic. The model also provides evidence for a normalization of *d*-amphetamine-induced abnormal behavior by administration of haloperidol. The well-known antagonism by haloperidol, and other DA receptor blocking agents, of *d*-amphetamine-induced hyperlocomotion or stereotypies [*e.g.* 40], is not accompanied by observations indicating that normal behavior has been restored.

Table 1. The discriminative avoidance procedure provides a double dissociation of effects produced by inhibition or overstimulation of brain dopaminergic neurotransmission. The two doses of α-methyl-*p*-tyrosine methylester HCl (H 44/68)(α-MT) were administered 20 and 4h before observations, respectively. *L*-DOPA (or saline) was given 1h before the observations. All animals were also given an inhibitor of peripheral aromatic amino acid decarboxylase (MK-486) 30 min before *L*-DOPA, or at a corresponding time in saline controls. For further details see text and [2]

	α-MT (250 + 50 mg kg^{-1}) pretreatment + *L*-DOPA (mg kg^{-1}) treatment		
Behavior parameter	0 (inhibition)	10 (normal)	100 (overstimulation)
Avoidance	+	0	0
Discrimination	0	0	+

0 No effect; *+* Effect

Effects of phencyclidine and kynurenic acid

Phencyclidine (PCP), initially developed as an anaesthetic, is like *d*-amphetamine a drug of abuse and can also in vulnurable individuals produce the symptoms of schizophrenia [30, 31]. Laboratory studies have provided evidence for similar actions by *d*-amphetamine and PCP on brain dopaminergic neurotransmission as a common denominator for their psychotomimetic effects [see 10]. Of potentially greater interest, however, are results from a number of studies suggesting effects by PCP outside the dopaminergic system and the possibility that the psychotomimetic effects of PCP are mediated by such other effects. Thus, specific DA receptor blocking agents have been less effective in antagonizing PCP-induced effects than those induced by *d*-amphetamine or apomorphine. Furthermore, in drug discrimination studies, *d*-amphetamine and PCP provide separate cues to the animals. Finally, in some clinical studies, it has been difficult to antagonize PCP-induced psychosis by conventional treatment with DA receptor blocking antipsychotics such as haloperidol [see 26].

On this background there were at least two good reasons to investigate the effects of PCP in the present test model. Firstly, to compare its effects with those found with *d*-amphetamine, as described above, and secondly, to examine the mechanism for possible effects obtained. As shown in Fig. 3 (top), it was found that PCP (2 mg kg^{-1}), like *d*-amphetamine, disrupted the performance of the visual discrimination without affecting avoidance behavior. There was also a statistically significant increase in the number of inter-trial crosses (Fig. 3, bottom). In contrast to its effects in the *d*-amphetamine experiment, however, the administration of the DA receptor antagonists haloperidol (0.1–0.2 mg kg^{-1}) or remoxipride (8 mg kg^{-1}) did not antagonize the PCP-induced abnormal behavior. It is also interesting to note, that unlike the effects of haloperidol on inter-trial crosses in the *d*-amphetamine experiments, haloperidol appeared to increase the number of inter-trial crosses in PCP-treated animals, an effect

that was statistically significant in animals given remoxipride (Fig. 3, bottom) [19]. Thus, phenomenologically PCP behaved as *d*-amphetamine in the discriminative avoidance procedure. The effects of haloperidol, however, appeared to be different. There was no antagonism of the disruption of discriminative behavior and, in contrast to results from *d*-amphetamine experiments, the psychomotor activation appeared augmented by the treatment. These observations are in line with the suggestion that the haloperidol – PCP interactions could be due to effects at the intercept between dopaminergic and glutamatergic mechanisms in the striatum [see 15].

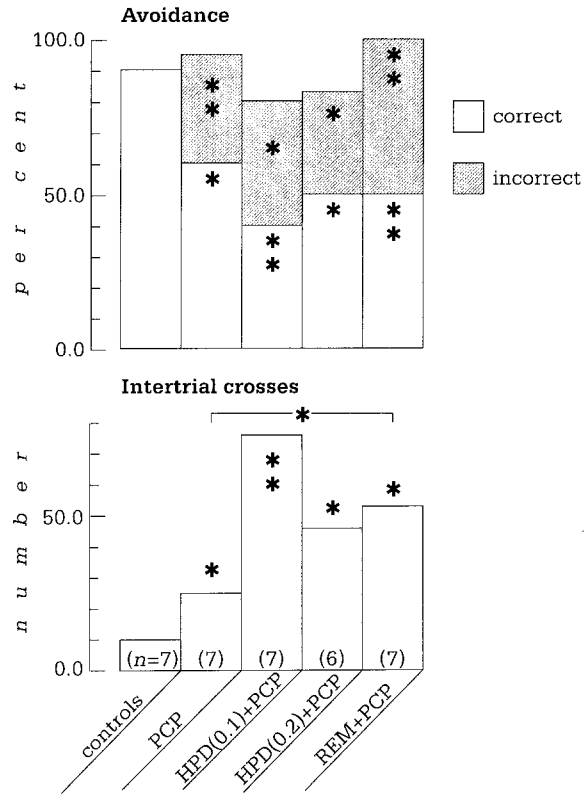


Fig. 3. Failure to antagonize phencyclidine-induced disruption of a successive visual discrimination by haloperidol or remoxipride administration in the rat. Phencyclidine (2 mg kg^{-1} SC), haloperidol (0.1 or 0.2 mg kg^{-1} SC) and/or remoxipride (8 mg kg^{-1} IP) were administered 20, 40 and 90 min before the observations, respectively. For further details see Legend to Fig. 1 [from 19]. $^{*}p < 0.05$, $^{**}p < 0.025$

In addition to its effects on the dopaminergic system, PCP also is an antagonist at brain *N*-methyl-*D*-aspartate (NMDA) receptors [see 18]. In order to test the possibility that such effects were responsible for effects by PCP on the visual discrimination we examined the effects of a specific, although not selective, excitatory amino acid antagonist, kynurenic acid [see 36]. As can be seen in Fig. 4, this compound, administered intracerebrally into the ventral forebrain (coordinates in relation to bregma, midline and brain surface, +2.1, ±1.2 and

+6.8 mm, respectively), produced the same pattern of effects as *d*-amphetamine and PCP: loss of discriminative performance and an increased number of inter-trial crosses. The general level of activity, as observed in an open field in a separate experiment, was not affected, however (Fig. 4) [20].

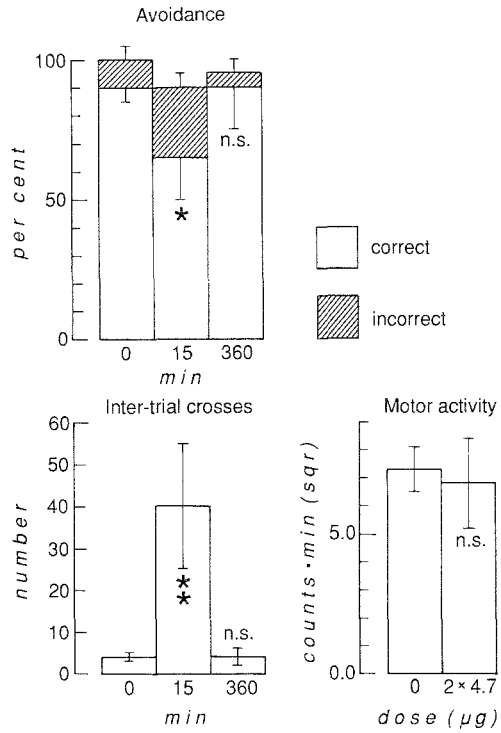


Fig. 4. Disruption by kynurenic acid of the performance of a visual successive discrimination, and effects on open field motor activity, in the rat. Kynurenic acid was locally applied into the nucleus accumbens (4.7 μg side^{-1}) and the animals ($n = 10$) were observed 15 and 360 min after the injection. Results are presented as medians $\pm$ semi-interquartile range, except for open field motor activity which is shown by mean $\pm$ SD ($n = 6$). Statistical analysis was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test or, in the case of motor activity measurements, by the Student's *t*-test [from 20]. $^{n.s.}p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.025$

Interruption of firing and release in dopaminergic neurons as a common denominator for behavioral effects by d-amphetamine and phencyclidine

Pharmacological release of DA, as induced by high doses of *L*-DOPA or the direct DA receptor stimulation produced by apomorphine results in an abnormal behavioral activation in rats, as described at the beginning of this paper. A pharmacologically induced DA release or direct receptor activation is in all probability not modulated by the nerve impulse flow and important feed-back mechanisms.

A great variability in firing patterns is a characteristic feature of the meso-limbic dopaminergic projection, in contrast to the nigro-striatal neuronal population. Thus, there is a high burst activity in the former but not in the latter,

which normally has a more pacemaker-like activity [25]. There is evidence to suggest that the DA release is specifically increased during burst activity [22–24]. Naturally, such mechanisms should not be in operation in case there is a drug-induced pharmacological DA release and/or excessive DA receptor stimulation by agonists. Interestingly, PCP has been shown both to increase the rate of firing in DA meso-limbic A10 neurons and to reduce burst activity [37]. This effect is similar to that observed by intracerebroventricular administration of the excitatory amino acid antagonist kynurenic acid [24], suggesting that the effects produced by PCP and kynurenic acid are mediated via excitatory amino acid receptors. The effects of high doses of *d*-amphetamine on brain dopaminergic neurotransmission are in all probability due to effects at the postsynaptic DA receptor as also evidenced by the fact that neuronal firing in this case is markedly decreased [12].

Bringing together the observations on the behavioral effects of excessive postsynaptic DA receptor stimulation and of excitatory amino acid antagonism on brain dopaminergic neurotransmission, we are left with two possibilities. Firstly, the possibility that the psychotomimetic effects of *d*-amphetamine and PCP are related primarily to a disruption of normal patterns of DA release and, secondly, that the effects of PCP, at least to some extent, are mediated on the output side of the dopaminergic neuron. Needless to say, a disruption of the physiological patterning of neuronal firing and neurotransmitter release could be a common denominater for the behavioral effects of both compounds even if such effects are exerted at different levels in a functionally interconnected network.

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