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Phencyclidine Does Not Disrupt Latent Inhibition in Rats: Implications for Animal Models of Schizophrenia

INA WEINER[1] AND JORAM FELDON

Department of Psychology, Tel-Aviv University, Ramat-Aviv, Tel-Aviv, Israel 69978

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WEINER, I. AND J. FELDON. *Phencyclidine does not disrupt latent inhibition in rats: Implications for animal models of schizophrenia.* PHARMACOL BIOCHEM BEHAV **42**(4) 625-631, 1992. – Latent inhibition (LI) is a behavioral paradigm in which prior exposure to a stimulus not followed by reinforcement retards subsequent conditioning to that stimulus when it is paired with reinforcement. The development of LI reflects a process of learning to ignore, or tune out, irrelevant stimuli. Three experiments investigated the effects of phencyclidine (PCP) on LI. The investigation was carried out using a conditioned emotional response (CER) procedure consisting of three stages: preexposure, in which the to-be-conditioned stimulus, tone, was repeatedly presented without reinforcement; conditioning, in which the preexposed stimulus was paired with shock; and test, where LI was indexed by animals' suppression of licking during tone presentation. The three stages were conducted 24 h apart. In Experiment 1, 1 mg/kg PCP was administered either in the preexposure or in the conditioning stage or in both. Experiment 2 used 5 mg/kg PCP in the same procedure. In Experiment 3, 5 mg/kg PCP was administered throughout the LI procedure, including the test stage. In all three experiments, PCP did not affect LI. The implications of these findings for the development of animal models of schizophrenia are discussed.

Latent inhibition Phencyclidine Schizophrenia Conditioned suppression Rat

ANIMAL models of schizophrenia typically rely on the administration of drugs that are known to produce and exacerbate psychotic symptoms in humans. The most prominent model of this kind is the animal amphetamine (AMPH) model of schizophrenia (55,57). It is widely accepted that AMPH-induced behavioral alterations in animals, as well as its psychotomimetic effects, are subserved by the augmentation of dopamine (DA) release, and the latter action has played a central role in the formulation of the dopamine hypothesis of schizophrenia. The most frequently studied behavioral effects of AMPH in animals are hyperactivity, produced by relatively low doses of the drug, and stereotypy, produced by higher doses. Since one of the central characteristics of schizophrenia is an attentional deficit, most often described as an inability to ignore irrelevant or unimportant stimuli [for a recent review, see (4)], Solomon et al. (60) and Weiner et al. (75-77) sought to demonstrate a similar deficit in AMPH-treated rats using the paradigm of latent inhibition (LI). In the LI paradigm, nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus when it is paired with reinforcement (39). For example, if an animal is preexposed to a series of tones, these tones lose their capability to enter into associations with other stimuli, such as shock, or responses such as shuttle avoidance. This decremental process is considered to reflect a process of learning not to attend to, ignore, or tune out irrelevant stimuli (41,43-45,49).

Systemic administration as well as direct injection of AMPH into the nucleus accumbens (NAC), the target of the ascending mesolimbic DA projection, were found to disrupt LI, and this disruption was suggested to model a schizophrenic-like inability to ignore irrelevant stimuli (60, 61,75-77). In support of this suggestion, it was shown that AMPH-induced disruption of LI is antagonized following DA receptor blockade by neuroleptic drugs (60,71,78) and that neuroleptics on their own markedly enhanced the LI effect (15,20,23,26,73,74). Furthermore, the extension of LI studies to the clinic revealed that LI is absent in acute schizophrenics tested within the first week of the beginning of a schizophrenic episode, but is reinstated after their psychosis diminishes with neuroleptic treatment (6). This finding renders the LI model

[1] To whom requests for reprints should be addressed.

construct validity that is rarely attained in animal models (21). In addition, in a normal population LI is present in low "psychosis-prone" subjects but is absent in high "psychosis-prone" subjects (7,40). Finally, Gray et al. (30) reported that LI is disrupted in normal volunteers given oral AMPH. The above results provide converging evidence that the disruption of LI taps a DA-dependent attentional deficit that is relevant to the pathogenesis of schizophrenia [see (25,26,72)].

An additional drug that has been suggested as a model psychotomimetic because it produces and exacerbates psychotic symptoms is phencyclidine (PCP) (11,19,42,59). Because of the connection between PCP and schizophrenia, extensive research has focused on the effects of PCP on DA biochemistry and DA-mediated behaviors. PCP has many AMPH-like behavioral properties, including the production of hyperactivity and stereotypy, as well as AMPH-like biochemical actions, that is, facilitation of DA release and inhibition of DA reuptake (5,34,38). Mansbach and Geyer (46) showed that PCP disrupted sensorimotor gating as assessed by prepulse inhibition of the startle response, suggesting that this drug, similarly to AMPH, impairs the ability to screen or "gate" sensory input. On the other hand, there are considerable differences between AMPH and PCP intoxication in humans (2,5,36,51), and the discriminative stimulus effects produced by PCP are not shared with those produced by AMPH (5,8,9,53,69). In addition, many behavioral effects of PCP in animals are apparently nondopaminergic as they are not blocked by DA agonists [e.g., (10,22,27,29,53,62,65,66)].

The present experiments tested whether PCP would produce an AMPH-like disruption of LI using a conditioned emotional response (CER) procedure in rats licking for water that we used for the study of AMPH (76,77). The CER procedure consisted of three stages: preexposure, in which the to-be-conditioned stimulus, tone, was repeatedly presented without being followed by reinforcement; conditioning, in which the preexposed stimulus was paired with reinforcement, shock; and test, in which LI was indexed by animals' suppression of licking during tone presentation. In Experiment 1, 1 mg/kg PCP was administered either in the preexposure or in the conditioning stage or in both. This drug administration procedure enables to determine the locus of drug action on LI (24,77). By means of this procedure, we showed that AMPH disrupted LI only when given in both the preexposure and conditioning stages, but not when confined to either of them. Since 1 mg/kg PCP was found to leave LI intact, Experiment 2 used 5 mg/kg PCP in the same procedure. Also, this experiment yielded LI. However, since the results obtained hinted at a state-dependent effect of PCP, in Experiment 3 5 mg/kg PCP was administered throughout the LI procedure, including the test stage.

EXPERIMENT 1

METHOD

Subjects

Ninety-six male Wistar rats (Tel-Aviv University Medical School, Israel), approximately 4 months old, were housed one to a cage under reversed-cycle lighting for the duration of the experiment. Upon delivery, subjects were maintained on ad lib food and water for 2 weeks. On the fifteenth day, all animals were weighed and placed on a 23-h water restriction schedule that continued throughout the experiment.

Apparatus

The apparatus consisted of two plastic test chambers set in a ventilated sound-insulated Grason-Stadler Research Chest (Model 1101). The internal dimensions of each chamber were 15 × 20 × 17 cm as measured from the grid floor. The chambers were flat grey, with small holes drilled in the side for ventilation. A drinking bottle could be inserted into the chamber through a 2-cm diameter hole 1.2 cm above the grid floor and 3 cm from the right side of the chamber. When the bottle was not present, the hole was covered by a plastic lid. Licks were detected by a Campden Instruments drinkometer circuit (Model 453). The preexposed to-be-conditioned stimulus was a 5-s 2.8-kHz tone produced by a Sonalert module (Model SC 628). The shock grid was made from stainless steel bars 0.25 cm in diameter with 1.5-cm intervals. Shock was supplied by a Campden Instruments scrambled-shock generator (Model 521C) set at 0.5 mA for a duration of 1 s. A Micro-Vax minicomputer was used for equipment programming and data collection.

Procedure

The stages of the CER procedure were as follows.

Baseline. For 10 days, rats were individually placed into the experimental chamber and allowed to make 600 licks. The subject was then returned to its home cage and an hour later allowed access to water for 30 min.

Preexposure. With the bottle removed, each animal was placed in the experimental chamber. Preexposed (PE) animals received 40 5-s tone presentations with a variable intertrial interval (ITI) of 60 s (VI 60). Nonpreexposed (NPE) animals were confined to the chamber for an identical period of time but did not receive the tones.

Conditioning. With the water bottle removed, each animal was given two tone-shock pairings. Tone parameters were identical to those used in preexposure. The 0.5-mA, 1-s shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. Five minutes later, the second pairing was administered. After the second pairing, animals were left in the experimental chamber for an additional 5 min.

Test. Each animal was placed in the chamber and allowed to drink from the bottle. When the subject completed 90 licks, the tone was presented. The tone continued until 10 additional licks were completed. If the subject failed to complete the last 10 licks within 300 s, the session was terminated and a score of 300 was recorded. The times between licks 80–90 and 90–100 were recorded. The times to complete licks 90–100 were subjected to logarithmic transformation to allow the use of analysis of variance (ANOVA). The stages of preexposure, conditioning, and test were given 24 h apart.

Drug Injections

The appropriate drug treatment, either 1 mg/kg PCP dissolved in 1 ml isotonic saline or an equivalent volume of saline, was administered IP 15 min prior to the start of preexposure and/or conditioning. The test stage was conducted without drugs.

Animals were randomly assigned to one of eight experimental groups in a 2 × 2 × 2 factorial design with main factors of stimulus preexposure (0,40), drug in preexposure (vehicle, PCP), and drug in conditioning (vehicle, PCP). Data of two subjects from the vehicle-vehicle PE group were lost due to apparatus failure. Thus, the final analyses were run on 94 subjects.

RESULTS

A 2 × 2 × 2 ANOVA with main factors of preexposure (0,40), drug in preexposure (vehicle, PCP), and drug in conditioning (vehicle, PCP) carried out on the mean times to complete licks 80–90 in the absence of the tone yielded no significant outcomes (all Fs < 1). The mean times in seconds to complete licks 80–90 in the eight groups were: vehicle-vehicle NPE, 2.33; vehicle-vehicle PE, 2.18; PCP-vehicle NPE, 1.78; PCP-vehicle PE, 2.37; vehicle-PCP NPE, 2.45; Vehicle-PCP PE, 2.43; PCP-PCP NPE, 1.97; PCP-PCP PE, 1.66. Figure 1 presents the mean log times to complete licks 90–100 in the presence of the tone for preexposed and nonpreexposed animals in four drug conditions in preexposure and conditioning: vehicle-vehicle, PCP-vehicle, vehicle-PCP, and PCP-PCP. As can be seen, LI was present in all four drug conditions, that is, the preexposed groups exhibited less suppression of drinking (poorer CER acquisition) than nonpreexposed groups. This outcome was supported by a 2 × 2 × 2 ANOVA with main factors of preexposure (0,40), drug in preexposure (vehicle, PCP), and drug in conditioning (vehicle, PCP) carried out on the mean log times to complete licks 90–100, which yielded a significant main effect of preexposure, $F(1, 86) = 10.87$, $p < 0.002$. A closer inspection of Fig. 1 reveals that the LI effect was larger in the two drug conditions in which PCP was administered in conditioning. This outcome was supported by the significant drug in conditioning × preexposure interaction, $F(1, 86) = 4.37$, $p < 0.04$. None of the other main effects of interactions were significant.

EXPERIMENT 2

METHOD

Subjects

Sixty-four male Wistar rats were used as in Experiment 1.

Procedure

The procedure used was identical to that used in Experiment 1.

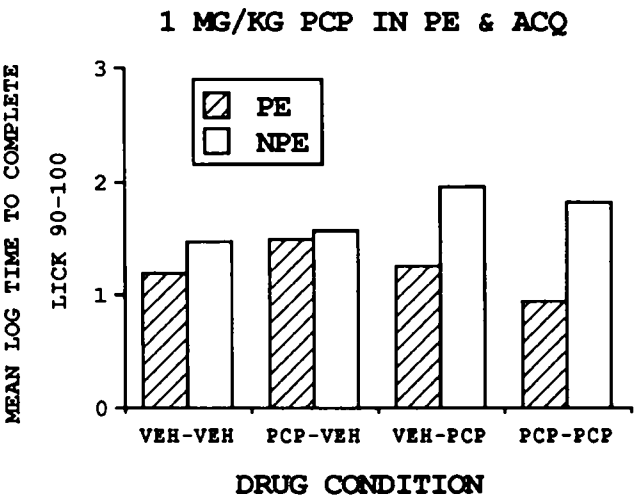

FIG. 1. Mean log times to complete licks 90–100 (tone on) of the preexposed and nonpreexposed groups under four drug conditions in preexposure and conditioning: vehicle-vehicle (VEH-VEH), phencyclidine-vehicle (PCP-VEH), vehicle-phencyclidine (VEH-PCP), and phencyclidine-phencyclidine (PCP-PCP). The dose of PCP was 1 mg/kg.

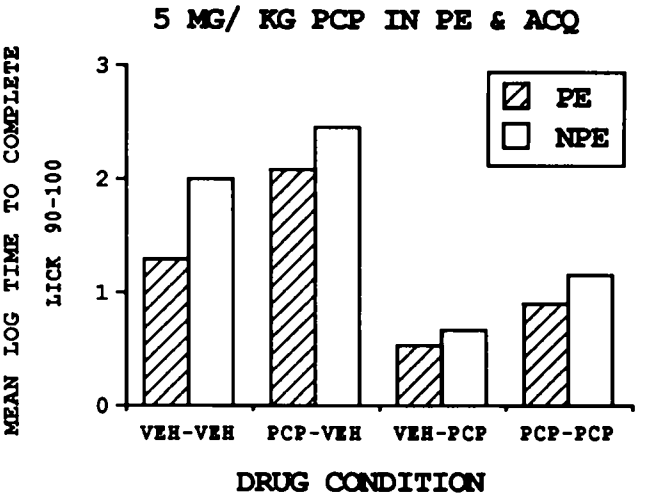

FIG. 2. Mean log times to complete licks 90–100 (tone on) of the preexposed and nonpreexposed groups under four drug conditions in preexposure and conditioning: vehicle-vehicle (VEH-VEH), phencyclidine-vehicle (PCP-VEH), vehicle-phencyclidine (VEH-PCP), and phencyclidine-phencyclidine (PCP-PCP). The dose of PCP was 5 mg/kg.

Drug Injections

Drug injections were as in Experiment 1, but the dose of PCP was 5 mg/kg. Animals were divided randomly into eight groups of eight subjects each as in Experiment 1. The data of one subject from the PCP-vehicle NPE group were lost due to apparatus failure.

RESULTS

A 2 × 2 × 2 ANOVA with main factors of preexposure (0,40), drug in preexposure (vehicle, PCP), and drug in conditioning (vehicle, PCP) carried out on the mean times to complete licks 80–90 in the absence of the tone yielded no significant outcomes (all Fs < 1). The mean times in seconds to complete licks 80–90 in the eight groups were: vehicle-vehicle NPE, 2.89; vehicle-vehicle PE, 2.23; PCP-vehicle NPE, 2.76; PCP-vehicle PE, 3.27; vehicle-PCP NPE, 3.75; vehicle-PCP PE, 1.85; PCP-PCP NPE, 5.27; PCP-PCP PE, 2.65. Figure 2 presents the mean log times to complete licks 90–100 in the presence of the tone for preexposed and nonpreexposed animals in four drug conditions in preexposure and conditioning: vehicle-vehicle, PCP-vehicle, vehicle-PCP, and PCP-PCP. As can be seen, LI, that is, lower suppression of the preexposed as compared to nonpreexposed groups, was present in all four drug conditions. This outcome was supported by a 2 × 2 × 2 ANOVA with main factors of preexposure (0,40), drug in preexposure (vehicle, PCP), and drug in conditioning (vehicle, PCP), which yielded a significant main effect of preexposure, $F(1, 55) = 7.67$, $p < 0.01$. In addition, inspection of Fig. 2 reveals that the administration of PCP during the preexposure phase led to increased suppression, particularly in the PE group, whereas the administration of PCP during conditioning led to decreased suppression in both the PE and NPE groups. The former result was supported by the significant main effect of drug in preexposure, $F(1, 55) = 15.55$, $p < 0.001$, while the latter result was supported by the

significant main effect of drug in conditioning, $F(1, 55) = 74.19$, $p < 0.001$. None of the interactions were significant (all $F < 1$). Since this pattern of results suggested the presence of a state-dependency effect in animals transferred from drug in preexposure to no drug in conditioning, as well as in animals transferred from drug in conditioning to no drug in test, in Experiment 3 5 mg/kg PCP was administered throughout preexposure, conditioning, and test.

EXPERIMENT 3

METHOD

Subjects

Twenty-eight Wistar rats were used as in Experiment 1.

Procedure

The procedure used was identical to that used in Experiment 1.

Drug Injections

PCP 5 mg/kg or vehicle were administered 15 min prior to preexposure and conditioning and 2 h prior to test. A pilot study showed that 2 h after injection animals drank freely.

Animals were divided randomly into four groups of seven subjects each in a 2 × 2 factorial design with main factors of preexposure (0,40) and drug (vehicle, PCP). The data of two subjects from the vehicle-NPE and PCP-NPE groups were lost due to apparatus failure so the final analyses were carried out on 26 subjects.

RESULTS

A 2 × 2 ANOVA with main factors of preexposure (0,40) and drug (vehicle, PCP) carried out on the mean times to complete licks 80-90 in the absence of the tone yielded no significant outcomes (all $F < 1$). The mean times in seconds to complete licks 80-90 in the four groups were: vehicle NPE, 2.27; vehicle PE, 2.45; PCP NPE, 2.34; PCP PE, 1.67.

Figure 3 presents the mean log times to complete licks 90-100 in the presence of the tone for the preexposed and nonpreexposed animals in two drug conditions: vehicle and PCP. As can be seen, in both conditions the preexposed groups showed less suppression (poorer CER acquisition) than nonpreexposed groups. This difference, which constitutes the LI effect, was supported by a 2 × 2 ANOVA with main factors of preexposure (0,40) and drug (vehicle, PCP), which yielded a significant main effect of preexposure, $F(1, 22) = 10.00$, $p < 0.005$. In addition, the administration of 5 mg/kg PCP led to decreased suppression in both the PE and NPE groups. This effect was supported by the significant main effect of drug, $F(1, 22) = 10.25$, $p < 0.005$.

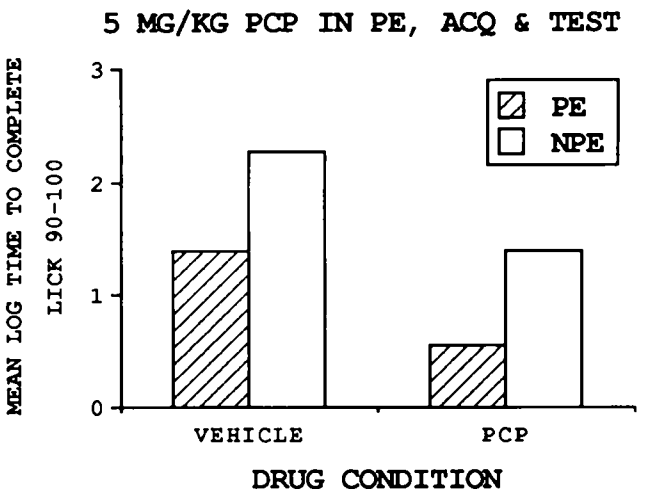

FIG. 3. Mean log times to complete licks 90-100 (tone on) of the preexposed and nonpreexposed groups under two drug conditions in preexposure, conditioning, and test: vehicle-vehicle (VEH-VEH) and phencyclidine-phencyclidine (PCP-PCP). The dose of PCP was 5 mg/kg.

GENERAL DISCUSSION

LI, that is, poorer conditioning to preexposed as compared to nonpreexposed stimulus, was unimpaired by both doses of PCP tested, 1 and 5 mg/kg. This outcome is particularly notable on the background of the effects exerted by PCP on conditioned suppression. In Experiment 1, the administration of PCP (1 mg/kg) in conditioning increased suppression of drinking in the NPE group, without producing a comparable increase in the PE group, thus not affecting, and in fact increasing, the LI effect (i.e., the difference between the NPE and the PE groups). In Experiments 2 and 3, the administration of PCP (5 mg/kg) reduced lick suppression in both the NPE and PE groups, yet the LI effect was preserved. Reduction of suppression produced by 5 mg/kg PCP in Experiment 3 (as well as in Experiment 2 when administered in conditioning, although this outcome was probably confounded with state-dependency effects) may reflect the antipunishment effect of PCP, which resembles that of benzodiazepines [(54), but see (56)]. However, PCP does not produce a benzodiazepine-like effect (24) on LI itself.

The failure of PCP to produce an AMPH-like disruption of LI provides additional evidence for the disparate behavioral effects of these psychogenic agents [e.g., (8,9,22,27,28,53, 58,65,69)]. Indeed, although some PCP-induced behaviors, as well as the psychomimetic effects of this drug, have been traditionally attributed to its indirect interactions with the DA system, it is by no means conclusive that this neurotransmitter mediates such effects (12,13,37). Particularly relevant to the present results is Geyer et al.'s (29) finding that PCP-induced disruption of sensorimotor gating is not antagonized by haloperidol. Recent research on the neurochemical pharmacology of PCP has shifted its focus to PCP's antagonism of the NMDA subclass of the glutamate receptor, and there is increasing evidence that this action can underlie most PCP-induced behaviors, including its motor stimulatory and psychotomimetic effects (12,13,37,48). Consistent with this possibility, Carlsson and Svensson (14) have shown that NMDA antagonists cause locomotor activation in monoamine-depleted animals, indicating that the stimulatory effects of these drugs may be mediated via a mechanism unrelated to the DA system. Of particular interest in the present context is the fact that DA-independent locomotor activation is characterized by an extreme inability to switch behaviors (e.g., to shift from forward locomotion to a different direction when an animal comes to a corner) (12) since we have argued that enhanced behavioral switching, caused by excessive DA release in the nucleus accumbens, subserves the AMPH-induced

disruption of LI (72). If reduction in glutamatergic transmission blocks the ability to switch behaviors (12), then this action may underlie the failure of PCP to produce an AMPH-like disruption of LI (see below).

The fact that PCP does not produce LI loss has important implications for the LI model and for the development of animal models of psychosis/schizophrenia in general. While it could be argued that this result undermines the validity of the LI model, we suggest the converse, namely, that it underlines the specificity and selectivity of this model. It is a truism that schizophrenia is a heterogeneous disorder, most probably underlied by different kinds of neurotransmitter imbalances. As emphasized by Claridge (16) and McKinney (47), this calls for a plurality of animal models, each limited to a particular aspect of the disorder. The disruption of LI by AMPH provides a DA-dependent, neuroleptic-sensitive model of a specific attentional deficit described in schizophrenia, namely, an inability to ignore irrelevant stimuli. This deficit is related to acute positive symptomatology since: a) AMPH produces and exacerbates positive symptoms but can improve negative symptoms (3,67,68); b) positive symptoms are associated with an incessant capturing of attention by irrelevant stimuli that are imbued with spurious significance [e.g., (4,18)]; and c) LI is absent in the acute stage of the illness and is restored by neuroleptic treatment (6).

In contrast to the above, Carlsson and Carlsson (13) and Swerdlow et al. (63) proposed that the behavioral stimulation and loss of prepulse inhibition, respectively, produced by NMDA antagonists via a catecholamine-independent mechanism provide an animal model of a DA-independent, neuroleptic refractory schizophrenia. In this context, it is important that PCP produces not only positive but also schizophrenia-like negative symptoms (2,36,50) and that the response of PCP-induced psychotic state to neuroleptic treatment is frequently poor (1,17,32,35). Piercey and Ray (51,52) and Tamminga et al. (64) showed, using 2-deoxyglucose autoradiographic technique, that in comparison to AMPH, which produces intense activation only in DA-rich areas, PCP dramatically altered metabolism also in the limbic system (Papez circuit) and that the latter effect was resistant to haloperidol (51,52). The PCP-induced alterations in the limbic system may be related to negative symptoms, such as blunting of affect and apathy.

In view of the above, it appears that AMPH and PCP may provide pharmacological models of neuroleptic-responsive positive and neuroleptic-nonresponsive negative symptomatologies, respectively. It remains to develop an animal model that produces a certain specific aspect of negative symptomatology. However, one possible approach to developing such a model could be derived from the evidence that whereas positive symptoms are associated with excessive switching of attention and high distractibility negative symptoms are characterized by an inability to switch attention and low distractibility (4,18,31,33,70). It will be recalled that the latter feature, that is, an inability to switch between different behavioral programs, is found in monoamine-depleted animals treated with NMDA antagonists. Thus, a blockade of behavioral switching may provide an animal correlate of negative symptoms. In fact, such a blockade can be demonstrated using the LI procedure. The development of LI is critically dependent upon the balance between the number of preexposures and the number of subsequent conditioning trials. Consequently, the number of tone-shock conditioning trials can be raised to a level at which normal animals cease to show LI, that is, switch to respond according to the stimulus-reinforcement contingency prevailing in conditioning. We would expect that animals whose capacity to switch behavior is disrupted following treatment with NMDA antagonists would continue to show LI under these conditions. A corollary of this prediction is that chronic schizophrenics with predominantly negative symptomatology should exhibit normal LI. Baruch et al. (6) found normal LI in chronic schizophrenics, but they were medicated. We would predict the same outcome in nonmedicated chronic patients.

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