

Research Report

Electrolytic lesions of the medial prefrontal cortex in rats disrupt performance on an analog of the Wisconsin Card Sorting Test, but do not disrupt latent inhibition: implications for animal models of schizophrenia

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Abstract

The effects of electrolytic lesions of the medial prefrontal cortex (mPFC) or its subregions were investigated on two cognitive tests that may have relevance to the behavioral impairments of patients with schizophrenia. One task consisted of a delayed non-match-to-sample and reversal of the non-match-to-sample rule, in a Skinner box. The reversal component simulated the essential feature of rule shifting of the Wisconsin Card Sorting Test (WCST), which is a commonly used test for assessing 'frontal-like' deficits in schizophrenia. The second was latent inhibition, in which repeated pre-exposure to a stimulus without consequence retards subsequent associations with that stimulus. Latent inhibition is impaired in acute schizophrenic patients, and its disruption in the rat has been suggested to constitute an animal model of schizophrenia. Expts. 1 and 2 tested the effects of lesions of the dorsal anterior cingulate cortex (dACA) and mPFC, respectively, on the WCST analog. Expt. 3 tested the effects of lesions of the dACA or infralimbic cortex, and Expt. 4 tested the effects of mPFC lesion, on latent inhibition. Lesions of mPFC subregions had no effect. mPFC lesion produced transient deficits in the performance of the DNMS task and impaired the reversal from the non-match-to-sample to the match-to-sample rule, but left the latent inhibition effect intact. Possible relevance of this behavioral profile of mPFC lesion to the 'frontal syndrome' is discussed.

Keywords: Frontal cortex; Medial prefrontal cortex; Dorsal anterior cingulate cortex; Infralimbic cortex; Learning; Delayed non-match-to-sample; Conditioned emotional response; Latent inhibition; Schizophrenia; Animal model; Psychosis; Rat

1. Introduction

The approach taken to the experimental study of schizophrenia in animals has relied on the development of pharmacological models based on the administration of drugs that produce and exacerbate schizophrenic symptoms in humans, or brain lesion models based on damage to areas implicated in the pathophysiology of this disorder. The most prominent model of the former kind is the animal amphetamine model of schizophrenia [36,45], while lesions to the hippocampus represent the latter kind of models [52,68,69].

Recently, there has been increasing interest in the

modeling of cognitive deficits in schizophrenia by paradigms that can be used in both humans and experimental animals. One such model is based on the paradigm of latent inhibition [24,29,56,67,95], in which repeated pre-exposure to a stimulus without consequence retards subsequent associations with that stimulus [53–56]. A recent review of human latent inhibition data has indicated that this phenomenon is similar in humans and animals, and can be viewed as reflecting the operation of analogous processes across species [56]. Latent inhibition is disrupted in rats by D-amphetamine [41,42,75,87,90,91,94,106], and this deficit is antagonized by neuroleptic drugs [87], whereas neuroleptic treatment on its own enhances the latent inhibition effect [13,18,43,65,92]. In parallel, it has been shown that latent inhibition is disrupted by amphetamine and enhanced by neuroleptics in normal humans ([31]; Williams et al., personal communication). The relevance

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of these findings to the behavioral impairments of schizophrenia has been demonstrated by the findings that latent inhibition is absent in acute schizophrenic patients [3,30,33], although recently, different results were reported [107]. Lesion studies of latent inhibition in the rat have indicated involvement of the hippocampal formation and adjacent cortical areas [1,9,37–39,74,78,82,97,103], as well as the nucleus accumbens [77,96], consistent with the central role attributed to medial temporal lobe and mesolimbic dopamine (DA) abnormality in schizophrenia (e.g., [10,88,89]).

While pharmacological evidence has implicated the dopaminergic system, and neuropathological and neuroimaging studies have tended to implicate parahippocampal and hippocampal cortex, there is also extensive evidence pointing to functional abnormality of prefrontal cortex (PFC), particularly the dorsolateral PFC (dlPFC), in schizophrenia. Such dysfunction has been shown most consistently in chronic schizophrenics ([2,6,10,47,57,88,89,102], but see [62]). The most commonly used test of dlPFC damage in humans is the Wisconsin Card Sorting Test (WCST) in which the subject is required to sort cards according to a certain rule (e.g., color), and change the rule based on error information [2,47,58,105]. Patients with schizophrenia, like frontal lobe patients, have difficulty in switching the sorting rule and continue to respond according to the previously correct solution [6,12,26,44].

The rat homolog of the dlPFC was suggested, on the basis of anatomical considerations, to be located in its medial prefrontal cortex (mPFC) [40,46,51,83]. This suggestion has been supported by behavioral studies of mPFC-lesioned rats which have shown that this area is involved in functions similar to those ascribed to human dlPFC, namely, rule learning and the ability to use and shift between different strategies (e.g., [48,49]). It thus appears that mPFC lesions can be used to model 'frontal-like' deficits of the kind reflected in disrupted WCST. The role of prefrontal cortex in latent inhibition has received little attention [8].

The present experiments had two aims: first, to assess the effects of frontal damage in rats on latent inhibition and on a task simulating the essential WCST feature of rule shifting; and second, to test whether the rat homolog of dlPFC can be more precisely localized.

Since the rat mPFC is a heterogeneous structure containing several cytoarchitectonically distinct subregions [84], it has been suggested that a more restricted area of the mPFC, namely, the pregenual shoulder area, is the rat homolog of dlPFC [83]. The shoulder area comprises two cytoarchitectonically different areas [84], namely, the agranular medial cortex (AGm) (or Fr2 of Zilles [104]) and the dACA. The AGm has been suggested to include areas homologous to the primate premotor cortex (PMC), supplementary motor area (SMA), and frontal eye field (FEF) [50,51,59,63,83].

In contrast to the AGm, the dACA has much weaker PMC-, SMA-, and FEF-like connections. For example, the dACA does not project to the medullary pyramids, nor to the brainstem motor nuclei and spinal cord [50], and its projections to primary visual cortex, the superior colliculus, and the oculomotor complex are weaker compared to those arising from the AGm [85]. Complementarily, the connections of the dACA are similar in several ways to those of the primate dlPFC. Both areas are connected with second-order association areas, posterior parietal cortex, premotor areas, and the second lateral segment of MD, and project to a homologous striatal region (rat [35,48,72,83,85], primate [27,48,70,71,83]).

In light of the above, we tested the possibility that the rat homolog of dlPFC is located in the pregenual dACA. Consequently, we tested the effects of dACA lesion on a WCST analog (Expt. 1) and on latent inhibition (Expt. 3). The WCST analog consisted of a reversal from a non-match-to-sample (NMS) to a match-to-sample (MS) rule in a Skinner box. Delayed non-match-to-sample (DNMS) is conventionally used to assess working memory deficits, by first training animals to acquire the NMS rule, and then testing the effects of delays on rule performance. We have added to this task the reversal component in order to test the ability to switch from the NMS to a MS rule. Latent inhibition was assessed using an off-baseline conditioned emotional response (CER) procedure in rats licking for water, consisting of three stages: pre-exposure, in which the to-be-conditioned stimulus (tone) was repeatedly presented without reinforcement; conditioning, in which the pre-exposed stimulus was paired with reinforcement (foot shock); and test, in which latent inhibition was indexed by the animals' degree of suppression of licking during tone presentation. Since dACA lesion had no behavioral effects, Expts. 2 and 4 tested the effects of larger mPFC lesions on these tasks.

2. Experiment 1. The effects of dACA lesion on delayed non-match-to-sample task and its reversal

2.1. Materials and methods

2.1.1. Subjects

Twenty-four male Wistar rats (Tel-Aviv University Medical School, Israel) approximately 4 months old, weighing 300–420 g, were housed in pairs under reversed cycle lighting. Upon arrival rats were maintained on ad libitum food and water for a month prior to surgery. One week before the beginning of behavioral testing, animals were fed approximately 1.5 h daily until their body weights were reduced to 85%. This weight level was maintained throughout the experiment. Water was freely available.

2.1.2. Surgery

Rats were anesthetized with an i.p. injection of Equithesin (3.0 ml/kg). They were placed in a stereotaxic frame and an incision was made into the scalp to expose the skull. The vertical coordinates of bregma and lambda were measured in order to align them in same (level head) plane. A small square of bone was removed starting approximately 1.5 mm anterior to bregma and extending rostrally about 3 mm. Bilateral electrolytic lesions were made by passing a 0.5-mA, 5-s current via a 0.3-mm electrode, insulated except for the tip. A constant (anodic) current DC source was used. Each animal was exposed to two anterior and two posterior lesions bilaterally. The coordinates were: anterior 3.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.5 mm ventral to dura; posterior 2.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.8 mm ventral to dura [64]. Control (sham-operated) animals underwent the same surgical procedure, but without the insertion of the electrodes. Sterispon was used to cover the hole in the bone, the scalp incisions were sutured by Michel clips, and sulfonamide powder was sprinkled on the wound. Animals were left to recover in their home cages for 14 days prior to the start of behavioral testing.

2.1.3. Apparatus

Behavioral tests were conducted in 8 operant chambers (Campden Instruments, UK), located four in a room, under on-line control of Compaq Prolinea 4/25 s computer. Each chamber was equipped with two retractable levers spaced 7.5 cm on each side of a central food tray that was accessed by a hinged perspex panel lighted from behind. A houselight was located at the center of the chamber ceiling and a food dispenser delivered 45 mg 'dustless' sucrose pellets (Campden Instruments).

2.1.4. Procedure

Adaptation to reward. During 3 days preceding the beginning of lever press training, rats were adapted to the food pellets in their home cages.

Lever press training. On the first 2 days, rats were trained to collect food pellets from the food tray in the operant chamber. Each session lasted 10 min, and every 20 s, a food pellet was delivered into the food tray, signaled by the panel light. Collection of the pellet extinguished the panel light, which was otherwise turned off after 10 s. The rats were then trained to lever-press on a continuous reinforcement schedule for 5 daily sessions. On days 1–3, each trial began with the insertion of both levers into the chamber which were retracted immediately after the rat made a response on one of them. Each response delivered a pellet, signaled by the panel light. Collection of the pellet started an intertrial interval of 15 s and extinguished the panel light, which was otherwise turned off after 10 s. A trial was defined

as a 'finished' trial if the rat pressed a lever and collected the food within 10 s. All other trials were recorded as 'unfinished'. Each session terminated after the rat completed 30 finished trials. On days 4–5, training continued as on days 1–3, but the levers were inserted one at a time, and remained until 15 finished trials were completed. This was done in order to prevent the establishment of side preference.

Delayed non-match-to-sample (DNMS) training. Following lever press training, rats were trained in the NMS procedure, consisting of 48 daily trials. Each trial included three components: sample response; delay interval; and choice response. At the start of each trial the house light was turned on and 2 s later the sample lever was inserted. The side of the sample (left or right) was determined in a pseudorandom order. As soon as the rat made a lever press response, the lever was retracted, the food-tray light was turned on and a food pellet delivered, and the delay interval began. The food-tray light was turned off when the rat collected the food. The delay component was terminated by the rat's first nose poke at the food-tray door after the completion of the delay interval. In the choice component, both levers were inserted into the chamber. A correct non-match response, i.e., to the lever not presented in the sample component, resulted in the levers being retracted, a food pellet delivered, and the food-tray light switched on until a further nose poke was made, indicating that the pellet was collected. An incorrect response, i.e., to the lever presented in the sample component, resulted in the levers being retracted, the house light switched off for 5 s (punishment), and no delivery of food. Following collection of the pellet on correct trials or punishment on incorrect trials, a 10-s intertrial interval preceded the next trial. A trial was defined as a 'finished' trial if the rat made a choice response (correct or incorrect). All other trials were recorded as 'unfinished'. In the first stage of training rats were trained with no delay between the sample and the choice components. Each rat was trained until it reached a criterion of at least 42 correct out of 48 finished trials on 3 consecutive days. After all rats had reached criterion at the NMS stage, they were trained for an additional 2 days, and on the subsequent day a variable delay interval schedule was introduced. On each trial, the delay was chosen at random from a range of delays. The range of delays was increased over a period of days from a range of 0- and 3-s delays, via a range of 0-, 3- and 6-s delays, to a range of 0-, 3-, 6- and 12-s delays. Training with each delay range continued until all animals performed less than 10 unfinished trials in a session and then the next delay range was introduced. Training on the final range of delays continued for 9 days.

Match-to-sample (MS) training. After completion of DNMS training, rats were run for two additional days with no delay. On the third day, MS training began.

Training was identical to that of NMS, but the correct response consisted of pressing the lever that was presented in the sample stage. Each rat was trained until it reached a criterion of at least 42 correct out of 48 finished trials on 3 consecutive days. The two experimental rooms were counterbalanced between the groups.

2.1.5. Measures and statistical analyses

Two response measures were recorded: (1) the number of days to reach criterion performance in the NMS (acquisition) and MS (reversal) stages; (2) percent of correct choices per daily session in the NMS and MS stages, and for each delay on each day during the DNMS stage. Arcsin transformation of the square root of the percent of correct choices was carried out on the raw data to allow analysis of variance.

The acquisition of the NMS and MS rules was assessed by two-way ANOVAs with main factors of room and lesion conducted on the number of days to criterion to acquire each rule, as well as by two-way ANOVAs with main factors of room and lesion and a repeated measurements factor of 3-day blocks conducted on the transformed correct choices. Performance of the two groups in the first day of introduction of each delay was assessed using two-way ANOVAs with main factors of room and lesion and a repeated measurements factor of delays. Performance on the final range of delays was assessed using two-way ANOVA with main factors of room and lesion and a repeated measurements factors of delays and 3-day blocks.

2.1.6. Histology

After completion of behavioral testing, lesioned animals were anesthetized with an overdose of Nembutal and perfused intracardially with physiological saline, followed by 10% formalin. Their brains were removed from the skulls and stored in 20% formalin–10% sucrose solution before being sectioned in the coronal plane at 80- μ m thickness. Every second section was mounted and stained with thionin blue for histological examination. Verification of placements used the atlas of Paxinos and Watson [64].

Twelve dACA and 12 sham-operated animals participated in the experiment.

2.2. Results

2.2.1. Anatomical

A representative reconstruction of the dACA lesions is presented in Plate 1, column A. The lesions obtained were triangular in shape in cross section and elongated in the anteroposterior axis. The lesions extended A–P 4.2–2.2 mm anterior to bregma in most of the animals. Restricted damage to the most dorsal aspect of the

prelimbic cortex and the most medial aspect of Fr2 was detected in most of the animals.

2.2.2. Behavioral

Fig. 1 (left side) presents the transformed percent correct choices, in three-day blocks, of the dACA and sham groups during the acquisition of the NMS rule. Two-way ANOVA conducted on these data yielded only significant effects of blocks $F(6,120)=66.21$, $P<0.0001$, and of the linear and quadratic trends of this factor $F(1,20)=146.01$, $P<0.0001$ and $F(1,20)=12.17$, $P<0.01$, respectively, reflecting similar rates of improvement in the two groups. Analysis of the number of days to criterion to acquire the NMS rule did not yield significant outcomes (sham, 17.22 (SE 1.66); dACA, 16.18 (SE 1.32)). Likewise, analysis of the transformed correct choices on the first day following introduction of the different delays (3, 6 and 12 s) yielded no significant outcomes.

Fig. 2 presents the transformed percent correct choices, in 3-day blocks, of the dACA and sham groups during the last 9 days of training with the final set of delays (0, 3, 6 and 12 s). Two-way ANOVA conducted on these data, revealed only significant effects of delay $F(3,60)=81.46$, $P<0.0001$ and of the linear and cubic trends of this factor, $F(1,20)=181.67$, $P<0.0001$, and $F(1,20)=10.63$, $P<0.01$, respectively, reflecting the fact that both groups made more errors at longer delays throughout training.

Fig. 1 (right side) presents the transformed percent correct choices, in 3-day blocks, of the dACA and sham groups during the acquisition of the MS rule following reversal. Two-way ANOVA conducted on these data, yielded only significant effects of blocks $F(10,200)=115.12$, $P<0.0001$ and of the linear, quadratic, and cubic trends of this factor, $F(1,20)=271.96$, $P<0.0001$, $F(1,20)=61.82$, $P<0.0001$, and $F(1,20)=20.84$, $P<0.001$, respectively, reflecting similar rates of improvement in the two groups following reversal. Analysis of the number of days to criterion after reversal did not yield significant outcomes (sham, 21.56 (SE 3.46); dACA, 19.73 (SE 1.31)).

2.3. Discussion

The performance of the dACA and sham rats in the acquisition, delay and reversal stages did not differ. There are no previous data on the behavioral effects of lesion restricted to the dACA, but larger mPFC lesions which included the dACA were reported to impair performance of a DNMS task [20,63], as well as other delay-type tasks (e.g., matching-to-sample task and spatial delayed alternation) [14,21,61,100,101]. None of these studies included a reversal stage. Consequently, Expt. 2 tested the effects of a larger mPFC lesion on the DNMS task and its reversal.

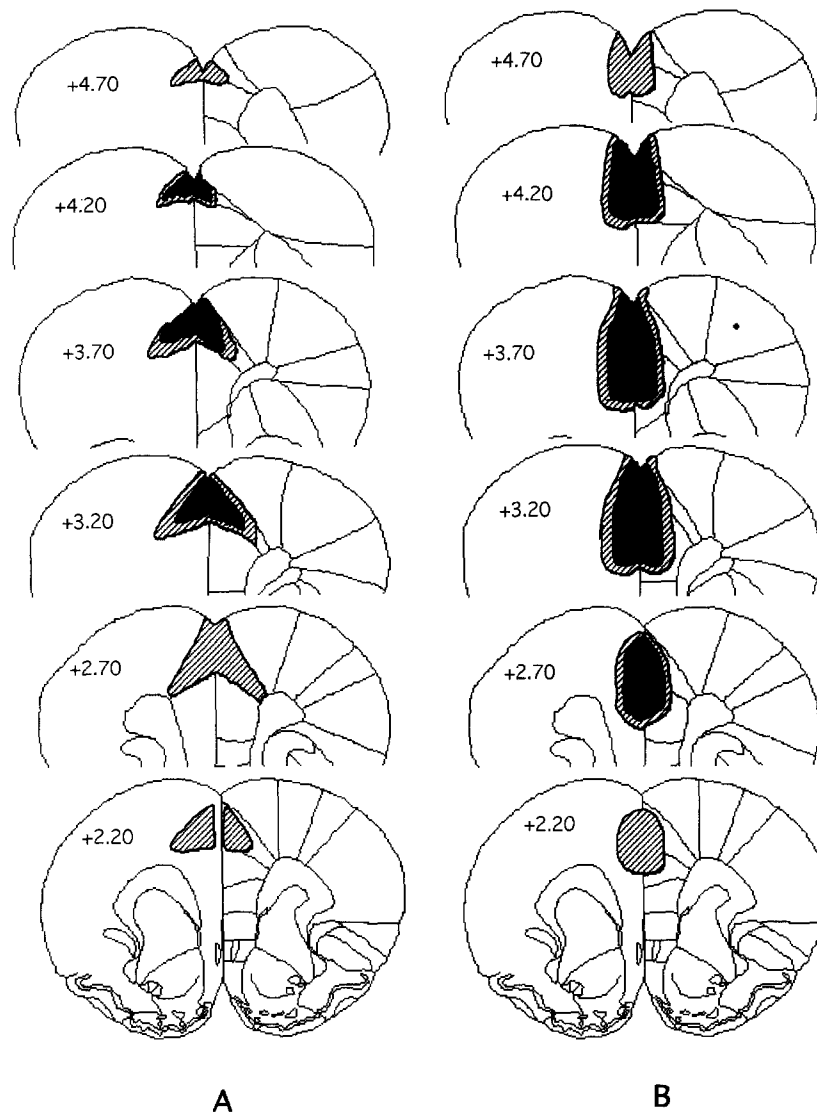


Plate 1. Reconstructions of dACA (column A, Expts. 1 and 3) and mPFC (column B, Expt. 2) lesions in successive brain sections taken from the atlas of Paxinos and Watson [64], representing the minimal extent (black) and the maximal extent (hatched) of the damage, in common for all rats in the group.

3. Experiment 2. The effects of mPFC lesion on delayed non-match-to-sample and its reversal

3.1. Materials and methods

3.1.1. Subjects

Twenty-four male Wistar rats were used as described in Expt. 1.

3.1.2. Apparatus, procedure, statistical analysis, and histology

Apparatus, procedure, statistical analysis, and histology were as in Expt. 1, except that the number of days on which the final set of delays was tested, was 20.

3.1.3. Surgery

The surgical procedure was identical to that of Expt. 1. Each animal was exposed to four anterior and four posterior lesions bilaterally. The coordinates were: anterior 3.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.5 and 2.7 mm ventral to dura; posterior 2.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.8 and 3.1 mm ventral to dura [64]. Control (sham-operated) animals underwent the same surgical procedure, but without the insertion of the electrodes.

Twelve mPFC and 12 sham rats began the experiment. One sham animal was dropped from behavioral testing because it did not learn to lever press, and one became ill during the experiment.

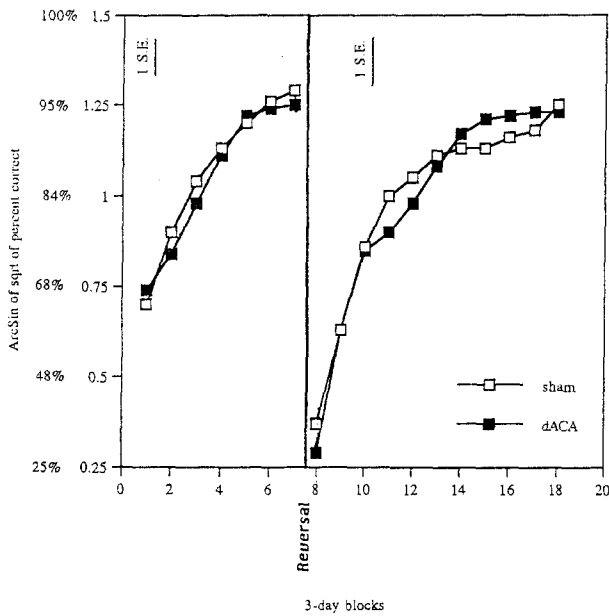


Fig. 1. The transformed percent correct choices, in 3-day blocks, of the dACA and sham groups during the acquisition of the NMS (left side) and MS (right side) rules. The corresponding percent correct choices are presented to the left of the transformation.

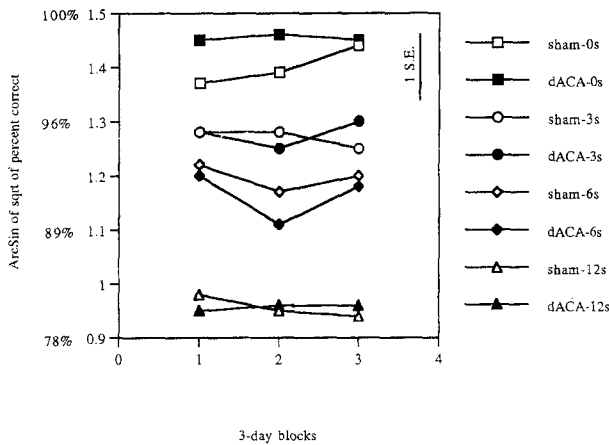


Fig. 2. The transformed percent correct choices, in 3-day blocks, of the dACA and sham groups during the last 9 days of training with the final set of delays (0, 3, 6 and 12 s). The corresponding percent correct choices are presented to the left of the transformation.

3.2. Results

3.2.1. Anatomical

A representative reconstruction of the mPFC lesions is presented in Plate 1, column B. The lesions obtained were rectangular in shape in cross-section and elongated in the anteroposterior axis. The lesions extended A-P 4.7-2.7 mm anterior to bregma in most animals. Restricted damage to the most medial aspect of Fr2 (AGm) was detected in most of the animals. One animal was excluded because of very short anteroposterior extent of the lesion. One animal was excluded because the damage to dACA was minimal. Thus, the final

analysis was performed on 10 mPFC and 10 sham animals.

3.2.2. Behavioral

Fig. 3 (left side) presents the transformed percent correct choices, in 4-day blocks, of the mPFC and sham groups during the acquisition of the NMS rule. A two-way ANOVA conducted on these data, yielded only significant effects of blocks $F(8,128) = 35.28, P < 0.0001$ and of the linear and quadratic trends of this factor $F(1,16) = 69.43, P < 0.0001$ and $F(1,16) = 14.64, P < 0.01$, respectively, reflecting similar rates of acquisition of the mPFC and sham groups. Analysis of the number of days to criterion to acquire the NMS rule did not yield significant outcomes (sham, 20.20 (SE 2.69); mPFC, 26.00 (SE 2.70)).

Following the introduction of the first (3 s) and second (6 s) delays, mPFC rats showed poorer performance than the sham rats at all delays (0 and 3 s and 0, 3 and 6 s, respectively). This was supported by two-way ANOVAs conducted on the transformed correct choices on the first training day with delays 0 and 3 s, and on the first training day with delays 0, 3, and 6 s, which revealed a significant lesion effect $F(1,16) = 5.12, P < 0.05$ and $F(1,16) = 5.70, P < 0.05$, respectively, and a significant repeated measurement effect of delay, $F(1,16) = 57.77, P < 0.0001$ and $F(2,32) = 11.14, P < 0.001$, respectively. mPFC rats did not differ from shams on the first day following the introduction of the last (12-s) delay. This was probably due to the poor performance of the sham animals following the introduction of this delay.

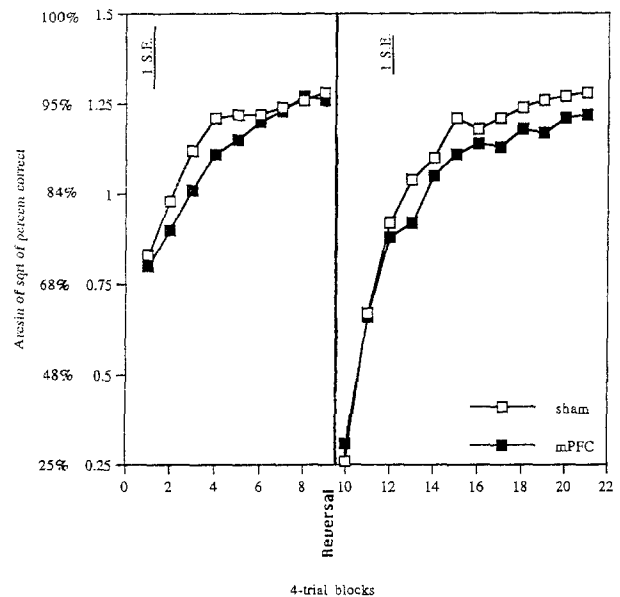


Fig. 3. The transformed percent correct choices, in 4-day blocks, of the mPFC and sham groups during the acquisition of the NMS (left side) and MS (right side) rules. The corresponding percent correct choices are presented to the left of the transformation.

Fig. 4 presents the transformed percent correct choices, in 4-day blocks, of the mPFC and sham groups during the last 20 days of training with the final set of delays (0, 3, 6 and 12 s). As can be seen, the performance of the two groups was similar: both groups improved their performance with training, especially at the 6 and 12 s delays, and made more errors at longer delays. This was supported by two-way ANOVA conducted on the transformed correct choices which revealed significant effects of delay $F(3,48)=90.72$, $P<0.0001$ and of the linear and quadratic trends of this factor $F(1,16)=173.32$, $P<0.0001$, and $F(1,16)=5.93$, $P<0.05$, respectively; significant effects of blocks $F(4,64)=16.36$, $P<0.0001$ and of the linear trend of this factor $F(1,16)=36.00$, $P<0.0001$; and a significant delay \times blocks interaction $F(12,192)=2.14$, $P<0.05$. However, it can be seen in Fig. 4 that the performance of the mPFC rats was poorer than that of sham rats at the end of training. Two-way ANOVA carried out on the last block, revealed a significant lesion effect $F(1,16)=7.03$, $P<0.05$, and significant effects of delay $F(3,48)=26.77$, $P<0.0001$ and of the linear trend of this factor, $F(1,16)=70.58$, $P<0.0001$.

Fig. 3 (right side) presents the transformed percent correct choices, in 4-day blocks, of the mPFC and sham groups during the acquisition of the MS rule following reversal. As can be seen, mPFC rats were slower to acquire the new MS rule. The number of days to reach criterion level of performance was greater for the mPFC group, and although the rate of improvement was similar for both groups, the mPFC rats performed less accurately throughout reversal training. This was supported by two-way ANOVA conducted on percent correct choices which revealed significant effects of lesion

($F(1,16)=6.89$, $P<0.05$), blocks ($F(11,176)=131.84$, $P<0.0001$), and the linear, quadratic, and cubic trends of this factor (all P -values <0.05), as well as by a two-way ANOVA conducted on the days to criterion of the two groups, which yielded a significant main effect of lesion $F(1,16)=5.27$, $P<0.05$ (sham, 31.70 (SE 4.02); mPFC, 40.40 (SE 4.39)).

3.3. Discussion

The results of Expt. 2 showed that: (1) mPFC rats did not differ from controls in the acquisition of the NMS rule; (2) by the end of training their performance at all delays was poorer compared to controls, but the impairment was not delay-dependent; (3) the introduction of the first and second delays resulted in a transient decline in performance at all delays; (4) mPFC rats took longer to reach criterion performance following the reversal of the NMS rule. The DNMS results are consistent with the claim that "no species with lesions in the PFC has escaped impairment of delayed response-type behaviors" ([17], p.173). Although impaired performance on delayed response tasks is often considered to reflect working memory deficit, a strict interpretation of a selective working memory impairment which can be separated from confounding lesion-induced alterations in learning capacity, motivational state, etc., requires a demonstration of delay-dependent disruption of performance [19,81]. Since the deficit exhibited by mPFC rats was not delay-dependent, the results indicate that mPFC lesion did not produce working memory impairment. Indeed, the strong conclusion regarding the central role of PFC in working memory has been based primarily on data from non-human primates (e.g.,

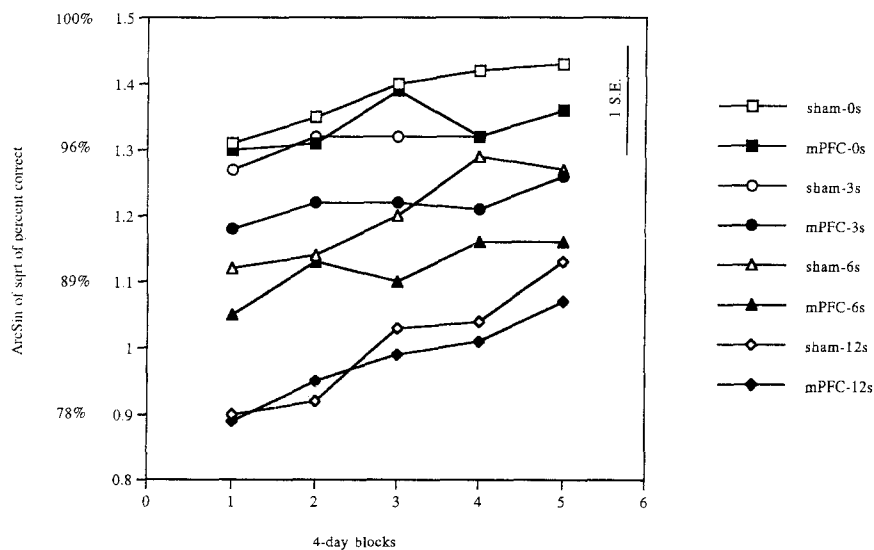


Fig. 4. The transformed percent correct choices, in 4-day blocks, of the mPFC and sham groups during the last 20 days of training with the final set of delays (0, 3, 6 and 12 s). The corresponding percent correct choices are presented to the left of the transformation.

[25,40,48,49,71]). There is less agreement in regard to the involvement of mPFC in working memory in rats. Results from delayed response tasks are consistent in demonstrating impaired performance, but are inconsistent regarding the dependence of the deficit on the delay (e.g., [20,46,61,80,100,101]), suggesting that mPFC rats may have a deficit in non-mnemonic aspects of these tasks. In other types of tasks testing working memory, such as the radial arm maze and the Maier's three table reasoning task, no deficit in working memory has been reported [46,66].

Slower reversal from the NMS to the MS rule exhibited by the mPFC rats suggests that these animals have difficulty in rule shifting. This suggestion is in line with the role attributed to the mPFC in rule learning and the ability to use and shift between different strategies, which is reflected in the inability of mPFC rats to learn more general aspects of a task, e.g., forming a learning set [5,46,99], changing their strategy when the situation changes [15,46,76], as well as using diverse strategies [16].

4. Experiment 3. The effects of dACA and infralimbic lesions on latent inhibition

Recent findings showed that latent inhibition is disrupted following lesions to the shell subterritory of the nucleus accumbens [77,96], which receives its major cortical input from the infralimbic cortex (IL) [35,72,83,85]. dACA projects to the medial caudate-putamen and not to the nucleus accumbens shell [35,72,83,85]. Therefore, although IL is not considered by some authors as part of mPFC (see [104]), Expt. 3 included a lesion of this region in addition to lesion of the dACA.

4.1. Materials and methods

4.1.1. Subjects

Fifty-four male Wistar rats were used as described in Expt. 1.

4.1.2. Surgery

The surgical procedure and dACA coordinates were identical to those of Expt. 1. Each IL animal was exposed to two anterior and two posterior lesions bilaterally. The coordinates were: anterior 3.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 3.5 mm ventral to dura; posterior 2.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 4.3 mm ventral to dura [64]. Control (sham-operated) animals underwent the same surgical procedure, but without the insertion of the electrodes.

4.1.3. Apparatus

The apparatus consisted of four Campden Instruments Rodent Test Chambers (Model 410), each set in a ventilated sound-attenuated Campden Instruments chest (Model 412). A drinking bottle could be inserted into the chamber through a 0.5-cm diameter hole which was at the center of the left wall of the chamber, 2.5 cm above the grid floor. When the bottle was not present, the hole was covered with a metal lid. Licks were detected by a drinkometer circuit (Campden Instruments drinkometer model 453). The pre-exposed to-be-conditioned stimulus was a 10-s, 2.8-kHz, 80-dB, tone produced by a Sonalert module (model SC 628). Shock was supplied by a Campden Instruments shock generator (model 521/S) set at 0.5 mA, 1 s duration. Equipment programming and data recording were controlled by an IBM-compatible personal computer (Amigo-MX).

4.1.4. Procedure

Handling. Prior to the beginning of the experiment, animals were handled for about 2 min daily for 6 days. A 23-h water restriction schedule was initiated simultaneously with handling and continued throughout the behavioral testing. Animals were allowed to drink for 1 h between 14.00 and 16.00 h.

The latent inhibition procedure included the following stages.

Baseline. On each of 5 days, each subject was placed into the experimental chamber and allowed to drink for 15 min.

Pre-exposure (PE). With the bottle removed, each animal was placed into the experimental chamber. The pre-exposed (PE) animals received 30 10-s tone presentations with a variable interstimulus interval of 50 s. The non-pre-exposed (NPE) animals were confined to the chamber for an identical period of time but did not receive the tone.

Conditioning. With the bottle removed, each animal was given two tone–shock pairings 5 and 10 min after the start of the session. Tone parameters were identical to those used in pre-exposure. The 0.5-mA, 1-s shock immediately followed tone termination. After the second pairing, animals were left in the experimental chamber for an additional 5 min.

Rebaseline. Each animal was given a drinking session identical to the baseline sessions.

Test. Each subject was individually placed in the chamber and allowed to drink from the bottle. When the subject completed 75 licks the tone was presented, and lasted 5 min. The following times were recorded: time to first lick, time to complete licks 1–50, time to complete licks 51–75 (pretone) and time to complete licks 76–100 (tone-on).

The stages of pre-exposure, conditioning, rebaseline

and test were given 24 h apart. Each subject was run throughout the experiment in the same chamber.

4.1.5. Experimental design

Fifty-four animals were randomly divided into six experimental groups in a 2×3 factorial design with main factors of pre-exposure (0, 30) and operation (sham, dACA, IL). Five animals (3 sham and 2 dACA) did not survive surgery.

4.2. Results

4.2.1. Anatomical

dACA lesions were very similar to those obtained in Expt. 1. A representative reconstruction of the IL lesion is presented in Plate 2, column A. The lesions obtained

were circular in shape in cross section and elongated in the anteroposterior axis. The lesions extended A–P 4.2–2.2 mm anterior to bregma in most animals. The lesion was restricted to the IL cortex (plates 8–10 in [64]) until it was replaced by the orbital cortex. Thus, more anteriorly (plate 7 in [64]) the lesions comprised the ventral prelimbic and dorsal medial orbital/ventral orbital (MO/VO), and in the most anterior aspect (plate 6 in [64]) the lesions comprised part of MO/VO. One animal was excluded because of very short anteroposterior extent of the lesion. Three animals were excluded because of damage to the dorsal peduncular cortex. Thus, the final analysis included 45 animals, with the following number of animals in each condition: sham-NPE, 7; sham-PE, 8; dACA-NPE, 7; dACA-PE, 9; IL-NPE, 7; IL-PE, 7.

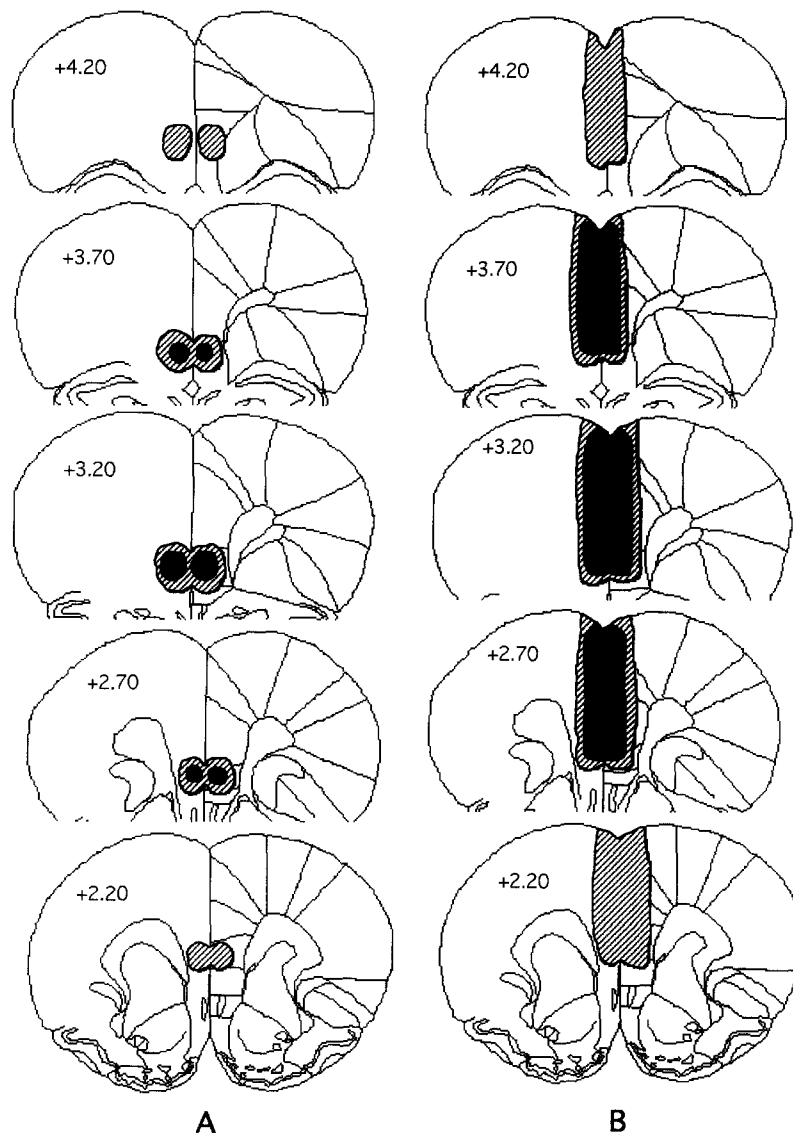


Plate 2. Reconstructions of IL (column A, Expt. 3) and mPFC (column B, Expt. 4) lesions in successive brain sections taken from the atlas of Paxinos and Watson [64], representing the minimal extent (black) and the maximal extent (hatched) of the damage, in common for all rats in the group.

4.2.2. Behavioral

Two-way ANOVAs with main factors of pre-exposure (0, 30) and operation (sham, dACA, IL) yielded no significant differences in the times to perform the first lick and to complete licks 1–50, and licks 51–75. The mean times to complete licks 76–100 in the presence of the tone in the three operation conditions are presented in Fig. 5. As can be seen, latent inhibition, i.e. shorter time to complete licks 76–100 of the pre-exposed as compared to the non-pre-exposed animals, was evident in all three conditions. This was supported by a two-way ANOVA with main factors of pre-exposure and operation performed on the data which yielded only a significant main effect of pre-exposure ($F(1,39) = 19.83$, $P < 0.0001$).

4.3. Discussion

In all three operation conditions, pre-exposed animals had shorter times to complete licks 76–100 in the presence of the tone than the non-pre-exposed animals, i.e., there was latent inhibition. The absence of a lesion effect on latent inhibition is particularly notable with regard to IL which provides the main cortical input to the nucleus accumbens shell, the lesion of which abolishes latent inhibition [77,96]. The present results suggest that the input from the IL to the shell is not critical to the presence of latent inhibition. This contrasts with disruption of latent inhibition obtained following lesions of the hippocampus [38,39,74] and entorhinal cortex [103], which provide another major source of input to the shell. Since the PFC is strongly implicated in schizophrenia [2,10,57,62,86,88,89,102], and there is evidence that small mPFC lesions may have no behavioral effects in tasks that are sensitive to larger lesions (e.g., [22,73,77,80], Expts. 1 and 2 of the present study), Expt. 4 tested the effects of a larger mPFC lesion on latent inhibition.

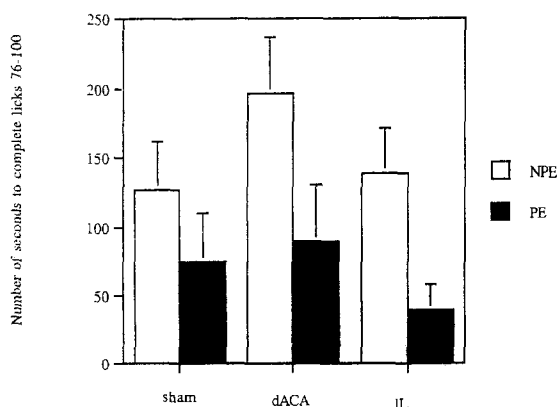


Fig. 5. Means and standard errors of the times to complete licks 76–100 in the presence of the tone in the pre-exposed (PE) and the non-pre-exposed (NPE) groups in the three operation conditions: sham, dACA and IL.

5. Experiment 4. The effects of mPFC lesion on latent inhibition

5.1. Materials and methods

5.1.1. Subjects, apparatus, procedure, statistical analysis, and histology

Subjects, apparatus, procedure, statistical analysis, and histology were as described in Expt. 3.

5.1.2. Surgery

The surgical procedure was identical to that of Expt. 1. Each mPFC animal was exposed to six anterior and six posterior lesions bilaterally. The coordinates were: anterior 3.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.5, 2.5 and 3.5 mm ventral to dura; posterior 2.7 mm anterior to bregma, 0.8 mm lateral to the midline, and 1.8, 3.0 and 4.3 mm ventral to dura [64]. Control (sham operated) animals underwent the same surgical procedure but without the insertion of the electrodes.

5.1.3. Experimental design

Eighty-eight rats were divided randomly into four experimental groups in a 2×2 factorial design with main factors of pre-exposure (0, 30) and operation (sham, mPFC). Data of three sham animals were lost due to apparatus failure.

5.2. Results

5.2.1. Anatomical

A representative reconstruction of the mPFC lesions is presented in Plate 2, column B. The lesions obtained were rectangular in shape in cross-section and elongated in the anteroposterior axis. The lesions extended A–P 4.2–2.2 mm anterior to bregma in most of the animals. Restricted damage to the most medial aspect of Fr2 (AGm) was detected in most of the animals. One animal was excluded because of very short anteroposterior extent of the lesion. One animal was excluded because of damage to the dorsal peduncular cortex. One animal was excluded because the damage to dACA was minimal. Thus, the final analysis included 82 animals, with the following number of animals in each condition: sham-NPE, 20; sham-PE, 21; mPFC-NPE, 22; mPFC-PE, 19.

5.2.2. Behavioral

Two-way ANOVAs with main factors of pre-exposure (0, 30) and operation (sham, mPFC) yielded no significant differences in the times to perform the first lick and to complete licks 1–50 and licks 51–75. The mean times to complete licks 76–100 in the presence of the tone in the two operation conditions are presented in Fig. 6. As can be seen, in both conditions, pre-exposed animals

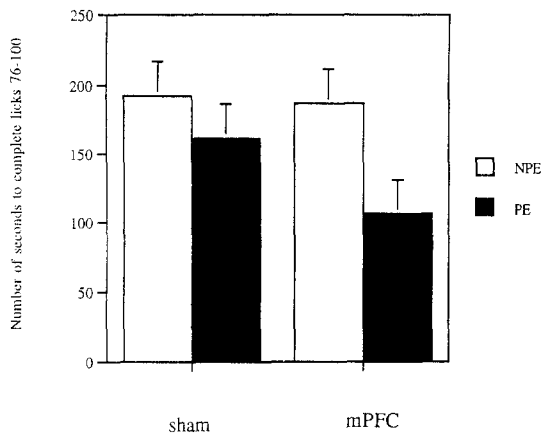


Fig. 6. Means and standard errors of the times to complete licks 76–100 in the presence of the tone in the pre-exposed (PE) and the non-pre-exposed (NPE) groups in the two operation conditions: sham and mPFC.

had shorter times than the non-pre-exposed animals, i.e., there was latent inhibition. This was supported by a two-way ANOVA with main factors of pre-exposure and operation conducted on the data which yielded only a significant main effect of pre-exposure ($F(1,78) = 5.85$, $P < 0.05$).

5.3. Discussion

Latent inhibition was not affected by a large mPFC lesion, suggesting that the integrity of this area is not critical for this phenomenon. Given the strong evidence for DA involvement in latent inhibition [29,32,34,95], there is a possibility that disruption of this phenomenon could be obtained with manipulations that directly affect the mPFC dopaminergic system. However, this does not seem to be the case, as no effects on latent inhibition were found in a recent study that directly injected DA agonists or antagonists into the mPFC [8]. Thus, injection of apomorphine decreased conditioned suppression in both the PE and NPE groups, but left the latent inhibition effect intact. Following an injection of *cis*-flupenthixol there was no latent inhibition, but this disruption was entirely due to decreased suppression in the non-pre-exposed animals. Thus, it appears that direct DA manipulations in the mPFC also do not affect latent inhibition. Intact latent inhibition following mPFC lesion is noteworthy in view of the often noted similarity between the effects of mPFC and hippocampal lesions, because it suggests that the latent inhibition phenomenon can dissociate between these lesions.

6. General discussion

dACA lesion did not affect the acquisition of the DNMS task or its reversal. The fact that a larger mPFC

lesion (which included in addition the prelimbic cortex) was effective, raises the possibility that some critical volume of tissue damage had to be attained for the observed behavioral effects, or that the prelimbic cortex is the critical site. In any event, the results obtained with the DNMS task do not support the suggestion that the rat dACA is a dIPFC homolog. No conclusions can be drawn in this respect from the latent inhibition experiments, since in this case, also the larger mPFC lesion was without consequence. In a different study, we found that dACA and mPFC lesions resulted in impaired learning in a 4-arm baited 8-arm radial maze task, compared with sham-operated rats. The analysis of the pattern of errors exhibited by the lesioned rats suggested that the impairment reflected a difficulty of the dACA and mPFC rats in learning complex rules, or complex behavioral strategies. These results indicate that in some tasks, dACA lesions may mimic the effects of larger mPFC lesions. In view of the growing interest in the structure–function relationships of the different mPFC subregions [15], it is of interest to continue and elucidate the behavioral functions of the dACA.

Expt. 2 showed that mPFC lesion impaired animals' capacity to acquire the MS rule after being trained on a NMS rule. This indicates that mPFC-lesioned rats have difficulty in rule shifting, similar to the 'frontal-like' deficit exhibited by schizophrenics on the WCST [6,47,58]. In addition, the introduction of delays after training on the NMS rule resulted in poorer performance of mPFC rats at all delays. The latter outcome is unlikely to have reflected impaired working memory, since: (1) decreased accuracy of performance after the introduction of each delay disappeared with training; and (2) poorer performance of the mPFC rats by the end of training was not delay-dependent and was evident even with no delay. We suggest that also these impairments were due to a difficulty of mPFC rats in changing their strategy according to the changed demands of the task following introduction of delays.

It should be noted that although there are many reports of impaired reversal learning following mPFC lesions, there is an important distinction between these tasks and the present one. Whereas most tasks use reversal of a specific solution (as, for example, reversing the correct and incorrect stimuli in discrimination learning tasks) the present task used reversal of a general rule (i.e., from the NMS to the MS rule). Since the latter is impaired in frontal patients, as seen in their pattern of errors in the WCST [6,47,58], tasks like the present one, involving rule shifting, seem to provide a better analog to the WCST. The difficulty of mPFC rats to acquire and shift general rules has been demonstrated using other tasks as well. For example, there are several studies reporting that mPFC lesions impair acquisition of a reversal learning set, but do not impair reversal learning (e.g., [4,46,60]). Similarly, de Bruin et al. [15]

found that mPFC rats were impaired when the strategy required for successful solution was changed, but not when the specific solution was reversed.

In contrast to the DNMS task, lesion of the mPFC had no effect on latent inhibition, i.e., lesioned pre-exposed animals drank faster in the presence of the conditioned stimulus than their non-pre-exposed counterparts. It should be noted that the mPFC lesion tested with latent inhibition was larger than that tested with the DNMS, as it also included the IL.

Since the PFC dysfunction is considered to play a major role in the pathophysiology of schizophrenia [2,6,10,47,57,62,88,89,102], and disruption of latent inhibition has been proposed as an animal model of this disorder [29,34,75,91,95], the failure of mPFC lesion to abolish latent inhibition might seem surprising. However, the relationship between latent inhibition disruption and schizophrenia is complex. Thus, although acute schizophrenic patients, suffering from first psychotic breakdown or being in an acute stage of an otherwise chronic disorder, do not show latent inhibition [3,30,33], latent inhibition is present in chronic schizophrenics, irrespective of neuroleptic treatment. Indeed, Gray et al. [33] showed that latent inhibition is reinstated as a function of chronicity of the disorder. Interestingly, a similar inverse relationship exists between latent inhibition disruption and the dose of amphetamine. Thus, in both rats and humans, latent inhibition is disrupted by low doses of amphetamine, but is left intact by high doses of this drug [31,93,94]. Taken together, these results may be interpreted as indicating that latent inhibition disruption in rats can serve only as a model of acute psychosis. Alternatively, it is possible that spared latent inhibition following certain manipulations, e.g., mPFC lesions or high doses of amphetamine, may provide an animal analog to the reinstated latent inhibition in the chronic state of this disorder. As was noted in the introduction, 'frontal syndrome', as reflected in impaired WCST performance, has been associated mainly with the chronic state of the disorder ([2,10,57,86,88,89,102], but see [62]). Therefore, the behavioral profile of the mPFC lesion obtained here, namely, disrupted rule shifting and intact latent inhibition, may provide an animal analog to the chronic state of the disorder, characterized by disrupted WCST performance and intact latent inhibition.

Disruption of cognitive functions normally associated with damage to the prefrontal cortex has been reported in a number of neuropsychological disorders, such as Parkinson's disease and Huntington's disease (e.g., [7,11,23,79,98]). Thus, the 'frontal syndrome' does not seem to be unique to schizophrenia, but may result from damage to any station of the basal ganglia-thalamo-frontocortical circuitry. It remains to be tested whether intact latent inhibition is specific to the chronic stages of schizophrenia or is characteristic to the 'frontal

syndrome'. There are indications that latent inhibition is not disrupted in Parkinson's disease, and may be even enhanced [56], but this needs further study. Thus, it is possible that intact latent inhibition is not specific to the chronic stages of schizophrenia, but rather appears as part of the frontal syndrome, whereas disrupted latent inhibition is specific to the acute stages of this disorder. Given the evidence linking latent inhibition disruption to hyperdopaminergic state [29,34,95], it can be suggested that disrupted latent inhibition is an index of increased DA transmission which, in schizophrenia, occurs periodically on the background of PFC dysfunction [28].

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