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Research report

Early maternal deprivation reduces prepulse inhibition and impairs spatial learning ability in adulthood: No further effect of post-pubertal chronic corticosterone treatment

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Abstract

Prolonged maternal deprivation leads to long-term alterations in hypothalamic–pituitary–adrenal (HPA) axis activity, disturbances of auditory information processing and neurochemical changes in the adult brain, some of which are similar to that observed in schizophrenia. Here we report the adult behavioural effects of maternal deprivation (12 h on postnatal days 9 and 11) in Wistar rats on paradigms of auditory information processing (prepulse inhibition), sensitivity to dopamimetics (amphetamine-induced hyper-locomotion) and cognition (T-maze delayed alternation and Morris water-maze). In addition, we examined the long-lasting effect of chronic 21-day corticosterone treatment during the post-pubertal period (i.e., postnatal days 56–76) on each of these behavioural paradigms in maternally deprived and control rats. Behavioural testing commenced 2 weeks after the termination of corticosterone treatment. Maternal deprivation led to a significant reduction in PPI and impaired spatial learning ability in adulthood, but did not affect the behavioural response to amphetamine. Post-pubertal chronic corticosterone treatment did not have any major long-lasting effects on any of the behavioural measures in either maternally deprived or control rats. Our findings further support maternal deprivation as an animal model of specific aspects of schizophrenia.

Keywords: Schizophrenia; Animal model; Maternal deprivation; Corticosterone; Amphetamine; Prepulse inhibition; T-maze delayed alternation; Morris water-maze

1. Introduction

The early environment has a profound effect on the developing brain. Adverse experiences early in life can lead to permanent alterations in neural systems [25,44] and may increase vulnerability to the development of major mental disorders [15,48,57]. Animal studies have shown that the quality of maternal care affects the development of the hypothalamic–pituitary–adrenal (HPA) axis and leads to altered stress reactivity in adulthood [23,27,33]. Generally speaking, rat pups separated from the mother for prolonged periods of time during the neonatal period display an enhanced endocrine response to stress and increased anxiety-like behaviour in adulthood [18,23].

In addition to altering behavioural and neuroendocrine responses to stress, prolonged periods of maternal deprivation can lead to other neurobiological changes in the offspring that persist into adult life, including alterations in monoaminergic neurotransmitter systems [1,53,57]. Recently, a single 24-h period of maternal deprivation on postnatal day 9 in Wistar rats has been shown to lead to several abnormalities related to schizophrenia, which do not emerge until after puberty [10,11,46]. These abnormalities include disturbances in auditory information processing (i.e., prepulse inhibition (PPI), startle habituation and auditory sensory gating) and neurochemical changes in the hippocampus of adult rats; specifically, a reduction in the expression of brain-derived neurotrophic factor (BDNF) and two NMDA receptor subunits [46]. BDNF, along with other neurotrophic factors, regulates neuronal survival, differentiation and plasticity and thus has an important role in

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the development and maintenance of neuronal networks. Both BDNF and NMDA receptors are known to play an important role in spatial working memory [38,39], however, few studies have investigated the effect of this maternal deprivation paradigm on cognitive functioning in adulthood. Maternal deprivation has also been shown to lead to altered regulation of BDNF expression in response to acute stress [46], suggesting that early deprivation may result in a reduced ability to adapt, at least at the molecular level, to conditions of stress in adulthood.

Chronic exposure to stress can have detrimental effects on brain structure and function. In rats, repeated restraint stress or corticosterone administration for 21 days causes atrophy of apical dendrites and decreased dendritic branching of CA3 pyramidal neurons in the hippocampus [60,61], and suppression of neurogenesis in the dentate gyrus [36]. Other effects of chronic corticosterone administration include alterations in PPI [16,58] and spatial working memory impairment [28,37]. Chronic exposure to elevated levels of corticosterone has also been shown to reduce hippocampal mRNA and protein levels of BDNF and neurotrophic factor 3 (NT-3) [4,52]. Given the long-term effects of prolonged maternal deprivation described above, it seems reasonable to postulate that maternally deprived rats may be more sensitive to the effects of chronic stress or corticosterone treatment during adulthood.

The present study aimed to further characterize the long-term behavioural consequences of maternal deprivation on a range of measures of relevance to schizophrenia, including the following: (1) amphetamine-induced locomotor hyperactivity (a measure of subcortical dopamine release), (2) PPI, a model of sensorimotor gating mechanisms in the brain, (3) performance on the T-maze delayed alternation task, a measure of spatial working memory most associated with the medial prefrontal cortex and (4) performance on the Morris water-maze task, as a measure of spatial learning ability. Furthermore, we aimed to investigate whether maternal deprivation leads to an increased vulnerability of the brain to chronic corticosterone treatment during young adulthood, resulting in the expression of more severe behavioural deficits.

2. Methods and materials

2.1. Animals

Male and female Wistar rats were obtained from Animal Services of Monash University, Victoria, Australia or Animal Resources Centre, Canning Vale, WA, Australia. Animals were housed in plastic cages (32 cm × 42 cm × 21 cm) with wire lids in a temperature-controlled room (22 ± 2 °C) on a 12 h light–dark cycle (light period 6:00 a.m.–6:00 p.m.). Food and water was provided *ad libitum* and cages were cleaned on a weekly basis. Following a minimum period of 1 week after arrival at the laboratory, breeding groups of two females to one male were formed. Eight days later, males were removed and females were housed separately. Inspection for newborn litters was performed twice daily at 9:00 a.m. and 5:00 p.m. Litters found before 5:00 p.m. were considered born that day. The day of birth was labelled pnd 0. Litters found before 9:00 a.m. were labelled pnd 1. All litters were culled to a maximum of 12 pups shortly after birth. Litters containing fewer than five pups were omitted from the experiment.

The maternal deprivation protocol was modelled on the 24-h separation protocol used by Ellenbroek and colleagues on pnd 9 [9,11]. However, it has been previously documented that a single 24-h deprivation period can cause some mortality among pups [24]. A protocol consisting of two 12-h deprivation periods was therefore used in the present study. The maternal deprivation procedure consisted of separating the entire litter from the dam at approximately 9:00 a.m. for a 12-h period on pnd 9 and 11 (DEP). Non-deprived (NDEP) control pups were left undisturbed with the dam until weaning (pnd 21). Maternally deprived litters were removed from the dam on the appropriate postnatal day and placed in plastic cages (14.5 cm × 30 cm × 12 cm) containing bedding from the home cage. Litters were then placed on a heat pad (30 °C) in a separate room maintained at 22–25 °C. Neither food nor water was available during the deprivation period. After an initial period of explorative activity, the mothers and pups would spend most of the separation time sleeping in their cage. At the end of the deprivation period pups were placed back with the dam. To minimise the potential confounding effect of litter [21], each experimental group consisted of rats derived from at least three different litters. The total number of litters used for the NDEP group was 7 (male:female 40:42, ratio 0.95:1). The total number of litters used for the DEP group was 7 (male:female 51:32, ratio 1.6:1). The average sex ratio of all litters combined was thus 1.2:1 (M:F). After weaning, the male animals were housed in groups of two or three per cage and their body weights were measured twice weekly. Female animals were not used in these experiments.

2.2. Corticosterone pellet implants

Previous studies have shown that maternal deprivation-induced behavioural changes do not emerge until after pnd 60. To investigate the interaction between maternal deprivation-induced changes and chronic corticosterone treatment, corticosterone was therefore administered from pnd 56 to 76. On pnd 56, rats (mean body weight = 276 ± 5 g) received a 100 mg corticosterone (Cort) or cholesterol (Con) pellet implant for 21 days. This period (i.e., pnd 56–76) corresponds to the post-pubertal/young adult period in the rat [55]. Based on previous experiments in our laboratory [12], a 100 mg corticosterone pellet implant produces circulating levels of corticosterone that correspond approximately to those observed during moderate to high levels of stress [50,51]. Specifically, during the 21-day pellet implant, mean plasma (am) corticosterone levels were 245 ± 21 ng/ml in corticosterone-treated rats compared to 109 ± 27 ng/ml in cholesterol-treated rats [12].

Pellet implants were made using a protocol adapted from Meyer et al. [35]. These authors have shown the time-course of elevated circulating corticosterone levels after pellet implantation. Briefly, corticosterone (Sigma, Castle Hill, NSW, Australia) or cholesterol powder (Sigma, Castle Hill, NSW, Australia) was heated in a mould to 180 °C until molten. A small amount of peanut oil was added to render the pellets less brittle. Once cooled, pellets were weighed and trimmed to 100 mg. On the day of the surgery, rats were anaesthetised with an intra-peritoneal injection of sodium phenobarbitone (Nembutal, 60 mg/kg; Merial Australia, Rhone Merieux, Qld., Australia). The back of the neck was shaved and a small incision was made at the nape of the neck. Connective tissue was separated from the skin to create a small pocket. The pellet was then placed under the skin at least 2 cm caudal to the incision, which was then suture-closed with either individual box stitches or one to two surgical staple clips. Twenty-one days after implantation, the pellet implant was removed using a similar procedure. In order to avoid the direct consequences and to selectively investigate the long-lasting effects of chronic corticosterone treatment and its interaction with maternal deprivation-induced changes, behavioural measurements were conducted 2 weeks after removal of the corticosterone pellet implant.

2.3. Behavioural testing

At approximately 90 days of age, behavioural testing commenced. The first cohort of rats was tested for amphetamine-induced hyperactivity and prepulse inhibition of acoustic startle, in a randomised, cross-over design. The number of animals per experimental group was as follows: NDEP Con $n = 12$; NDEP Cort $n = 11$; DEP Con $n = 10$; DEP Cort $n = 10$. The second cohort of rats was tested for performance on the T-maze delayed alternation task, followed by the Morris water-maze task approximately 1 week later. The number of animals per experimental group was as follows: NDEP Con $n = 6$; NDEP Cort n = 5; DEP Con $n = 6$; DEP Cort $n = 5$.

2.4. Locomotor activity

Locomotor activity was monitored using eight automated photocell cages (31 cm × 43 cm × 43 cm, $h \times w \times l$, ENV-520, MED Associates, St. Albans, VT, USA). The position of the rat at any time was detected with 16 infrared sources and sensors on each of the four sides of the monitor. Distance moved in centimetres was calculated from the ambulatory counts, which consisted of a consecutive interruption of at least four beams within a period of 500 ms. Rats were allowed to habituate to the novel environment for a period of 30 min, after which each rat was injected subcutaneously in a randomised fashion with either saline (0.9%) vehicle or 0.5 mg/kg D-amphetamine (Sigma Chemical Co., St. Louis, MO, USA). D-Amphetamine was dissolved in 0.9% saline and administered at an injection volume of 1 ml/kg. Locomotor activity was assessed for a further 90 min after which the animals were returned to their home cage. Locomotor activity tests were performed with 3–4-day intervals to allow clearance of amphetamine. To assess pre-test habituation of locomotor activity, the average distance moved during the initial 30 min of the locomotor sessions was analysed in 5-min blocks. To assess amphetamine-induced locomotor hyperactivity, the total distance moved during the 90 min following injection of saline or amphetamine was analysed. One animal (NDEP, Cort) did not receive an amphetamine injection and was therefore removed from the locomotor analysis.

2.5. Prepulse inhibition of the acoustic startle response (PPI)

PPI experiments were performed using a four-unit automated SRLab startle system (San Diego Instruments, San Diego, CA, USA). Rats were placed individually into 9 cm diameter Perspex cylinders that were closed at either end. These cylinders were placed on a sensitive motion-detecting platform inside a sound-attenuating box with a background sound level of 70 dB. Sound stimuli were delivered through speakers in the ceiling of the box and responses were measured using the SRLab software (San Diego Instruments). Movement of the rats was measured during 100 ms after startle stimulus onset. Rats were allowed to habituate to the background noise for 5 min after being placed into the chambers. The protocol was adapted from methods developed by the group of Geyer and Swerdlow [14]. A total of 100 trials were delivered with an average (but not constant) interval of 25 s. The first and last 10 trials consisted of single 40 ms 115 dB startle stimuli. The middle 80 trials consisted of random delivery of twenty 115 dB startle stimuli, 10 trials during which no stimuli were delivered and 50 prepulse trials. The prepulse trials consisted of a single 115 dB startle stimulus preceded by 100 ms by a 20 ms non-startling prepulse stimulus of 2, 4, 8, 12, or 16 dB over baseline (i.e., 72, 74, 78, 82, or 86 dB). The entire session lasted approximately 45 min. The acoustic startle response (ASR) was determined as the mean startle amplitude (measured in arbitrary units) of all startle (115 dB) trials. PPI was determined according to the formula: 100 − (startle amplitude at prepulse trial)/(mean startle amplitude) × 100%. To facilitate data interpretation, we will only present average PPI here (i.e., the average of all five prepulse intensities).

2.6. T-maze delayed alternation

To increase motivation for food, rats were maintained at 90% of their pre-experimental body weight by feeding a limited amount of food until the end of the T-maze test. Food was distributed and body weights were taken on a daily basis. Rats were allowed free access to water at all times. The rats were initially habituated to the T-maze (dimensions: start box 26 cm length (L) × 26 cm width (W) × 15 cm height (H); stem arm 68 cm (L) × 12 cm (W) × 15 cm (H); branch arms 52 cm (L) × 12 cm (W) × 15 cm (H) each) for 4 days, until they were readily eating food rewards at each end of the branch arms. After habituation, rats were trained and tested on a delayed alternation task based on a method described previously [40]. Rats were given daily training sessions consisting of 11 consecutive trials in which the rat was required to alternate between the left and right arm in order to obtain a food reward consisting of a single Kellogg's Fruit Loop. On the first trial (forced trial), access to one of the two arms was blocked, forcing the rat to enter the other arm that contained a food reward; the direction of the forced trial was alternated daily. On the subsequent 10 trials, the rat was rewarded only for entering the arm not chosen on the previous trial (free-choice trial). A correct trial ended with the rat eating the food reward. An incorrect trial ended with the rat reaching the empty food cup. If the rat did not enter into the arm within 2 min, the trial was not counted and the rat was given another attempt. After each trial, the rat was removed from the branch arm and placed in the start box ready for the next trial. The criterion for successful completion of training was defined as >80% correct turns averaged over two to three consecutive days. Once the criterion was reached, spatial delayed alternation was tested by interposing a 30- or 60-s delay period between the trials. During this time the rat was confined to the start box. Each delay period was tested for two consecutive days. The number of errors made and latency to find the food were recorded and averaged over the 2 days. The number of errors made (response accuracy) was taken as a measure of spatial working memory. The latency to reach the food reward was used to assess possible motivational or motor impairments.

2.7. Morris water-maze test

Spatial learning ability was assessed using the Morris water-maze test. The water-maze consisted of a large plastic pool (diameter 160 cm, height 62 cm) filled with water (24 °C) and 100 ml of non-allergenic, water-soluble black paint. A square, black platform (13.5 cm × 13.5 cm) was placed 2 cm beneath the opaque water and was therefore hidden from the animal's view. Rats were given four consecutive trials per day for 4 days in which to find the hidden platform using spatial cues on the wall. The spatial cues consisted of several different geometric shapes made of coloured cardboard. Rats were placed into the water, facing the wall of the tank, sequentially into four different entry points that were set equally around the pool (N, S, W and E). Thus, the rat was not able to predict the location of the platform from the point at which it was placed in the pool. The order of the four entry points was randomized between animals and days. The rat was then allowed to search for the platform for 60 s. Once the rat located the platform, it was permitted to remain on it for 20 s to allow orientation to visual cues in the room. If the platform was not located within the 60-s trial, the rat was guided to the platform by the experimenter. After each trial, rats were briefly dried with a towel (10 s) and the next trial began immediately. Upon completion of the last trial, rats were thoroughly dried (i.e., towel dried and placed under a heat lamp) and returned to their home cages. A video camera was mounted above the centre of the water-maze. The distance travelled (pathlength) and time taken (escape latency) to reach the hidden platform during the trials and the velocity (swim speed) were recorded by a computerized video tracking system (Ethovision, Noldus, The Netherlands). The pathlength and escape latency to reach the hidden platform was averaged over the four consecutive trials to give the mean pathlength and mean escape latency per day. The mean pathlength and mean escape latency over the four test days were taken as a measure of spatial learning ability. In order to assess motor, sensory or motivational deficits, on day 5, the platform was moved to a different quadrant and was made visible, rising 1 cm above the water surface. Rats received four consecutive trials in which to escape to the visible platform. Time taken to reach the visible platform was recorded.

2.8. Data analysis

The factorial design of the study was 2 (maternal deprivation: NDEP, DEP) × 2 (treatment: corticosterone, cholesterol). All data were analysed with analysis of variance (ANOVA) with repeated measures where appropriate, using the statistical software package SYSTAT 9.0 (SPSS Inc., Chicago, IL, USA). Where $p < 0.05$, group differences were considered to be statistically significant. 'Maternal deprivation' and 'corticosterone treatment' were between-subject factors. Within-subject factors included 'drug' (saline or amphetamine; locomotor activity test), 'delay period' (T-maze) and 'day of testing' (Morris water-maze). In case of a significant interaction, independent t-tests were performed to determine differences between groups.

3. Results

3.1. Body weight

Table 1 shows the effect of maternal deprivation and chronic corticosterone treatment on body weight. There was a slight, but

Table 1
Body weight (g) at weaning age (pnd 21) and at the start of behavioural testing (pnd 90) and amount of body weight gain during the pellet implant period (pnd 56–76)

Age (pnd)	NDEP		DEP	
	Con	Cort	Con	Cort
21	47 ± 1		44 ± 1	
56	278 ± 8	277 ± 10	281 ± 10	267 ± 12
BW gain during 56–76	87 ± 5	73 ± 5[a]	79 ± 4[b]	47 ± 9[a,b]
90	417 ± 12	412 ± 12	402 ± 14	374 ± 17

Data are presented as mean ± S.E.M. NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet; BW = body weight; pnd = postnatal day.
[a] $p < 0.01$ compared to NDEP.
[b] $p < 0.001$ compared to cholesterol treated.

non-significant effect of deprivation on pnd 21 ($F = 2.5$; d.f. = 1, 63; $p = 0.1$), reflecting lower body weights in DEP rats compared to NDEP rats. On pnd 56 (prior to the pellet implant), there was no difference in body weight between NDEP and DEP rats. There was no deprivation by treatment interaction on the amount of body weight gain during the pellet implant period, but there was a main effect of treatment ($F = 15.3$; d.f. = 1, 61; $p < 0.001$), and a main effect of deprivation ($F = 8.2$; d.f. = 1, 61; $p = 0.006$). As expected, corticosterone treatment reduced the amount of body weight gain during the pellet implant period. In addition, DEP rats, regardless of the type of pellet implant received, gained less body weight during the pellet implant period than NDEP rats. At pnd 90, at the start of the behavioural experiments, again there was a slight, but non-significant effect of deprivation ($F = 2.5$; d.f. = 1, 61; $p = 0.07$), reflecting lower body weights in DEP rats compared to NDEP rats.

3.2. Locomotor activity

3.2.1. Pre-test habituation

As expected, there was a significant main effect of time on locomotor activity during the initial 30 min of testing ($F = 161$; d.f. = 5, 190; $p < 0.001$), indicating habituation to the novel environment (Fig. 1). There were no three-way or two-way interactions and no main effect of deprivation on locomotor activity; a main effect of treatment did not reach significance ($F = 4.0$; d.f. = 1, 38; $p = 0.052$), but suggested slightly lower locomotor activity in corticosterone-treated rats.

3.2.2. Amphetamine-induced locomotor hyperactivity

Locomotor activity after injection of saline vehicle or amphetamine is illustrated in Fig. 1. Treatment with amphetamine significantly increased locomotor activity compared to vehicle treatment as shown by a main effect of drug ($F = 141$; d.f. = 1, 38; $p < 0.001$). There was no drug × deprivation × treatment interaction and no drug × deprivation interaction, but there was a trend for a drug × treatment interaction on locomotor activity ($F = 3.7$; d.f. = 1, 38; $p = 0.06$) (Fig. 1). This non-significant interaction reflected a tendency for corticosterone-treated rats to have lower

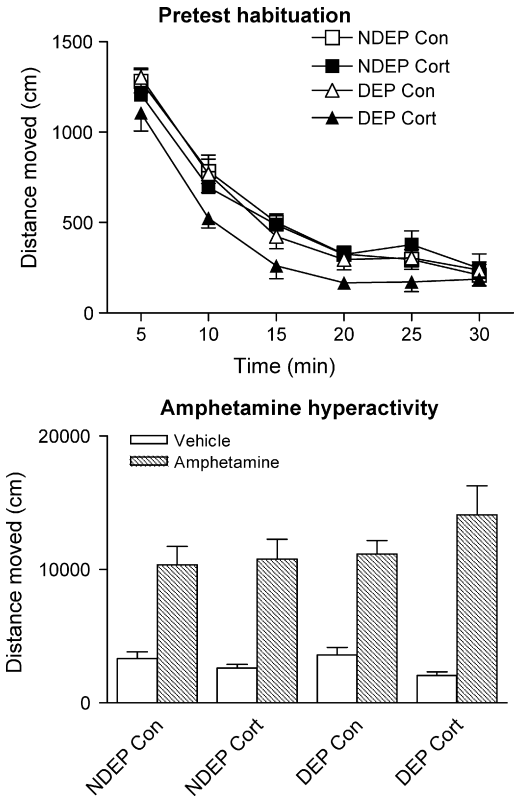

Fig. 1. Top graph: pre-test habituation of locomotor activity calculated as the average distance moved (cm) in 5-min blocks during the first 30 min of the locomotor sessions. Bottom graph: total distance moved during the 90 min after injection of saline vehicle (open bars) or 0.5 mg/kg of D-amphetamine (hatched bars). Data are presented as mean ± S.E.M. NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet.

and higher activity after injection of saline and amphetamine, respectively, compared to cholesterol-treated rats.

3.3. Prepulse inhibition of acoustic startle

3.3.1. Acoustic startle response (ASR)

There was no deprivation × treatment interaction and no main effect of corticosterone treatment or deprivation on the ASR (Fig. 2).

3.3.2. Prepulse inhibition of startle (PPI)

There was no deprivation × treatment interaction on PPI, however, there was a significant main effect of deprivation ($F = 6.0$; d.f. = 1, 39; $p = 0.019$). DEP rats had significantly lower PPI compared to NDEP rats (Fig. 2). There was no main effect of treatment on PPI. There were significant effects of prepulse intensity, but no interactions with either treatment or deprivation (not shown).

3.4. T-maze delayed alternation

3.4.1. Training sessions

Fig. 3 shows the number of sessions required in order to reach the criterion for successful completion of training (defined

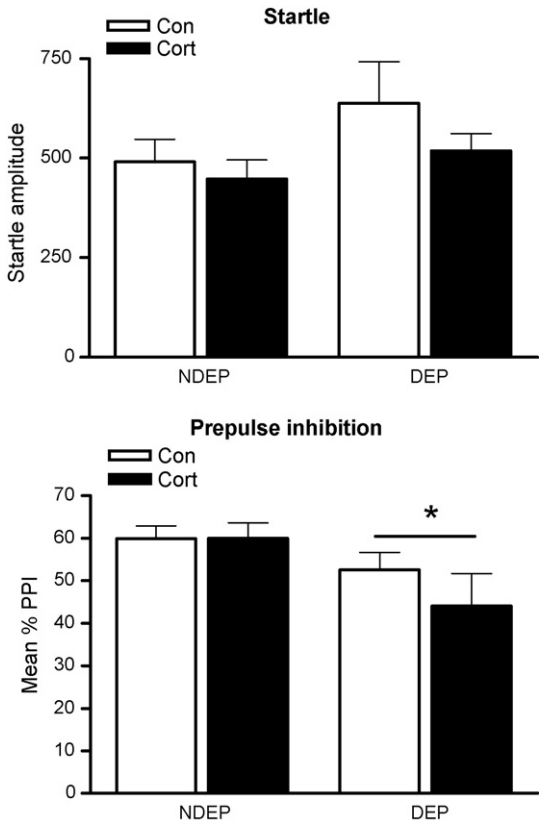

Fig. 2. Top graph: mean startle amplitude (arbitrary units) to a 115 dB startle stimulus. Bottom graph: mean percentage of prepulse inhibition of startle (PPI). Data are presented as mean ± S.E.M. NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet. $^{*}p < 0.02$ indicates main effect of deprivation, i.e., significant difference between combined DEP groups compared to NDEP groups.

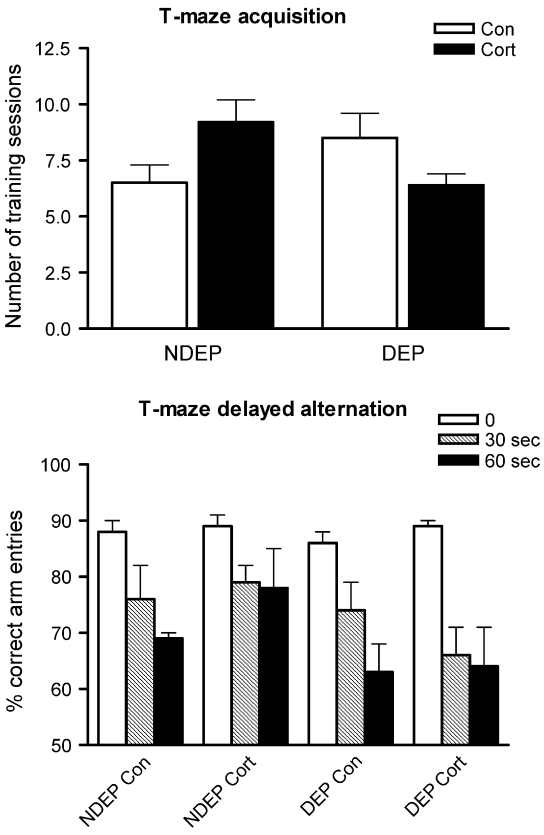

Fig. 3. Top graph: number of training sessions required for successful completion of training, defined as more than 80% correct entries on two to three consecutive days. Bottom graph: performance on the T-maze delayed alternation test: the percentage of correct arm entries are shown for the 0-, 30- and 60-s delay period trials. Data are presented as mean ± S.E.M. NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet.

as more than 80% correct entries on two to three consecutive days). There was a significant deprivation × treatment interaction ($F = 7.5$; d.f. = 1, 18; $p = 0.01$), but no main effect of deprivation or treatment on the number of training sessions required to reach the criterion. Further analysis revealed a trend for the NDEP corticosterone-treated group to require a higher number of training sessions compared to the NDEP control group ($p = 0.054$). There was no significant difference between DEP corticosterone-treated and DEP control rats in the number of training sessions required to reach the criterion.

3.4.2. Percentage of correct arm entries

Fig. 3 shows the percentage of correct arm entries for each of the delay period conditions. As expected, the percentage of correct arm entries decreased with increasing delay period between the trials, as shown by a main effect of delay period ($F = 25.3$; d.f. = 2, 36; $p < 0.001$). Both the 30 s delay period ($F = 31.1$; d.f. = 1, 18; $p < 0.001$) and the 60 s delay period ($F = 54.4$; d.f. = 1, 18; $p < 0.001$) significantly reduced the percentage of correct arm entries compared to the no delay period condition. There was no overall delay period × deprivation × treatment interaction, no significant two-way interactions and no main effect of treatment on the percentage of correct arm entries. However, there was a trend for a main effect of deprivation ($F = 4.1$; d.f. = 1, 18; $p = 0.059$), suggesting a lower percentage of correct arm entries in DEP rats (Fig. 3, bottom graph). Thus, in the combined NDEP controls and NDEP corticosterone-treated groups, the 30-s delay period reduced the number of correct entries by 1.1 ± 0.3, whereas in the combined DEP controls and DEP corticosterone-treated groups, this change was 1.7 ± 0.4 correct entries. Similarly, in the combined NDEP controls and NDEP corticosterone-treated groups, the 60-s delay period reduced the number of correct entries by 1.5 ± 0.3, whereas in the combined DEP controls and DEP corticosterone-treated groups, this change was 2.4 ± 0.4 correct entries.

3.4.3. Latency to reach food reward

Table 2 shows the mean latency to reach the food reward for each of the delay period conditions. There was no main effect of delay period between trials on the latency to reach the food reward, indicating that the delay period did not affect the rats' motivation to find the food reward. There was no delay period × deprivation × treatment interaction, no significant two-way interactions and no main effects on latency to reach the food reward, indicating that there were no motivational or motor impairments in any of the experimental groups.

Table 2
Latency to reach the food reward in the T-maze delayed alternation test of spatial memory

Delay period (s)	NDEP		DEP	
	Con	Cort	Con	Cort
0	2.3 ± 0.2	3.0 ± 0.4	3.8 ± 1.2	2.3 ± 0.2
30	2.6 ± 0.1	2.5 ± 0.2	3.0 ± 0.3	2.9 ± 0.2
60	2.9 ± 0.2	2.9 ± 0.3	3.0 ± 0.3	3.4 ± 0.9

NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet.

3.5. Morris water-maze

3.5.1. Pathlength to reach the hidden platform

Fig. 4 shows the mean pathlength to reach the hidden platform over the four testing days. There was a main effect of day on mean pathlength ($F = 29.1$; d.f. = 3, 54; $p < 0.001$), reflecting a reduction in the mean pathlength taken to reach the hidden platform over the four testing days. There was no day × deprivation × treatment interaction, no significant two-way interactions and no main effect of treatment, but there was a main effect of deprivation on mean pathlength ($F = 11.3$; d.f. = 1, 18; $p = 0.003$). DEP rats, on average, swam a significantly greater distance to reach the hidden platform compared to NDEP rats (Fig. 4).

3.5.2. Escape latency

Fig. 4 shows the mean escape latency to reach the hidden platform over the four testing days. Mean escape latency decreased over the four testing days, as shown by a main effect of day ($F = 24.3$; d.f. = 3, 54; $p < 0.001$). There was no day × deprivation × treatment interaction, no significant two-way interactions and no main effect of treatment, but there was a main effect of deprivation on mean escape latency ($F = 9.3$; d.f. = 1, 18; $p = 0.007$). DEP rats, on average, spent significantly more time searching for the hidden platform compared to NDEP rats (Fig. 4).

3.5.3. Mean velocity

Fig. 4 shows the mean velocity (i.e., swim speed) on each of the four testing days. There was no day × deprivation × treatment interaction, no significant two-way interactions and no main effect of deprivation or treatment on mean velocity, indicating that swim speed was not affected by deprivation or corticosterone treatment. There was a main effect of day on mean velocity ($F = 3.3$; d.f. = 3, 54; $p = 0.03$). This was due to a significantly higher mean velocity on day 2 compared to day 4 ($p = 0.01$). There were no significant differences in mean velocity between any of the other days.

On the visible-platform training day, all mean escape latencies were under 10 s and there were no significant differences in escape latency between any of the experimental groups (data not shown), indicating that there were no sensory, motor or motivational impairments.

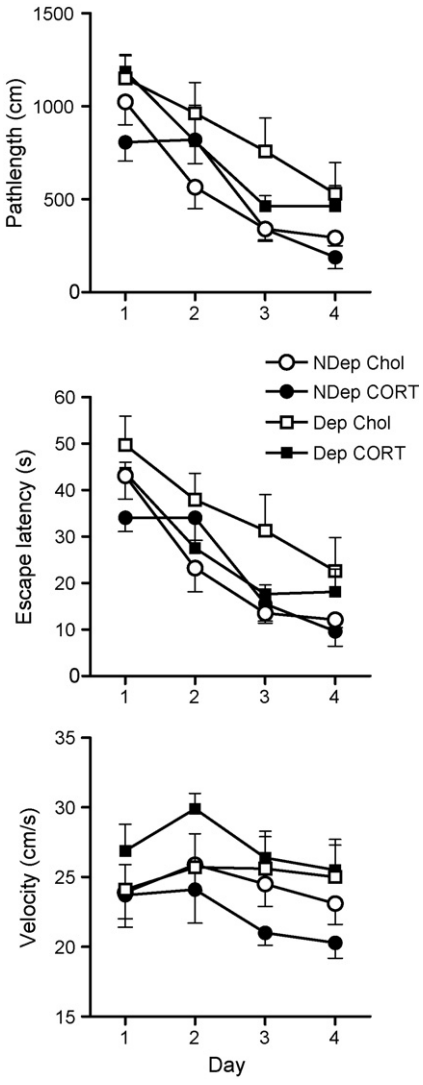

Fig. 4. Mean pathlength (top panel), mean escape latency (middle panel) and mean velocity (bottom panel) to reach the hidden platform over the four testing days in the Morris water-maze test of spatial learning ability. Data are presented as mean ± S.E.M. NDEP = non-deprived; DEP = maternally deprived; Con = cholesterol pellet; Cort = corticosterone pellet. There was a significant difference in pathlength and escape latency in DEP rats compared to NDEP rats ($p \leq 0.007$).

4. Discussion

Previously, it has been demonstrated that neonatal maternal deprivation can reproduce, in the adult rat, some of the features observed in schizophrenia patients and thus may represent an interesting animal model of certain aspects of schizophrenia. Specifically, maternal deprivation has been shown to lead to a disruption of prepulse inhibition (PPI) and startle habituation, reduced latent inhibition (a measure of selective attention) and a reduction in levels of neurotrophic factors in the hippocampus of post-pubertal, but not pre-pubertal rats [7,10,11,46]. Our data verifies and extends upon this literature by demonstrating a reduction in PPI, impaired spatial learning ability and a tendency for impaired spatial working memory (trend level only) in adult maternally deprived rats. Impaired cognitive performance

is a core feature of schizophrenia [42] and thus, the present findings further support maternal deprivation as an animal model of aspects of schizophrenia. Contrary to our hypothesis, however, chronic corticosterone treatment during the post-pubertal period (i.e., pnd 56–76) did not produce, or exacerbate, any behavioural deficits in maternally deprived rats.

4.1. Neonatal maternal deprivation

Consistent with previous findings [10,11], maternal deprivation resulted in a small, but significant reduction in PPI in adult Wistar rats. This reduction in PPI appeared to be slightly smaller in magnitude to that reported by Ellenbroek and colleagues, which may be due to differences in the maternal deprivation paradigm (i.e., a 12-h deprivation on pnd 9 and 11 versus a single 24-h deprivation period on pnd 9). Indeed, the effects of maternal deprivation are known to be highly dependent on the timing, duration and frequency of the deprivation period [21,57]. Mechanisms underlying the disruption of PPI caused by maternal deprivation remain to be identified. However, based on indirect evidence, it has been suggested that hyperactivity of the dopaminergic system may underlie the disruption in PPI in maternally deprived rats [11]. The PPI disruption caused by maternal deprivation appears to be similar to that produced by systemic administration of dopamine receptor agonists, such as apomorphine, and both are reversed by prior treatment with typical or atypical antipsychotic drugs [8,11,13,57]. In addition, alterations of the nigrostriatal dopamine pathway have been reported in maternally deprived rats [7,47]. In the present study, we found that maternal deprivation did not significantly alter amphetamine-induced locomotor hyperactivity (Fig. 1). Amphetamine-induced locomotor hyperactivity is mediated via release of dopamine in the nucleus accumbens [19] and thus our findings suggest that alterations in the mesolimbic dopamine system may not be primarily involved in the disruption of PPI observed in maternally deprived rats, although further studies are required to confirm this. To our knowledge, no other studies have examined the effect of a prolonged (>8 h) maternal deprivation on behavioural responses related to the mesolimbic dopamine system in adulthood.

Maternal deprivation also led to delayed acquisition of the Morris water-maze task, indicating an impairment in spatial learning ability, as well as a tendency for reduced performance on the T-maze delayed alternation task (a measure of spatial working memory), in adult rats. Few studies to date have investigated the effect of prolonged maternal deprivation on cognitive functioning in adulthood. Consistent with our findings, a single 24-h maternal deprivation on pnd 3 has been shown to lead to an impairment of spatial learning ability in the Morris water-maze task at 3 and 12 months of age [41]. However, a tendency for an improvement in water-maze learning in maternally deprived (24-h on pnd 9) adult rats, has also been reported [22].

Alterations in the expression of hippocampal BDNF levels and NMDA-R subunits may underlie, in part, the impairment in spatial learning ability observed in maternally deprived rats. As mentioned earlier, maternal deprivation (24-h on pnd 9) leads to decreased expression of BDNF and two NMDA receptor subunits in the hippocampus of adult rats [46], both of which have an important role in learning and memory processes [38,39]. In contrast, adult rats that have received a high level of maternal care (i.e., licking and grooming) during the neonatal period display an increased expression of NMDA receptor subunits in the hippocampus, which is accompanied by enhanced spatial learning and memory [26].

It is interesting to note that while a significant impairment in spatial learning ability was observed in the hippocampus-dependent Morris water-maze task in maternally deprived rats, only a small reduction (trend level) in spatial working memory was observed on the medial prefrontal cortex-associated T-maze delayed alternation task. This may reflect the relative anatomical specificity of maternal deprivation-induced changes in the hippocampus (a brain region that is particularly vulnerable to early environmental insults) compared to prefrontal brain regions. For example, while changes in the expression of BDNF and NMDA receptor subunits were evident in the PFC of maternally deprived rats, they were less consistent than in the hippocampus [46]. In future, it would be interesting to determine whether the deprivation-induced deficit in spatial learning ability only emerges after puberty, similar to that observed with the deprivation-induced changes in hippocampal BDNF and NMDA receptor expression [46]. As spatial learning ability has been shown to be indicative of performance in other spatial memory tasks and cognitive abilities [49], future studies should also determine whether maternally deprived rats display impairments on other memory-related tasks.

4.2. Post-pubertal chronic corticosterone treatment

In the present study, we were primarily interested in the sustained effects of chronic corticosterone treatment and its interaction with maternal deprivation-induced changes. Therefore, a 2-week recovery period was allowed following the termination of corticosterone treatment. Chronic corticosterone treatment did not cause a long-lasting (i.e., >2 weeks) disruption of PPI in non-deprived (control) rats and did not significantly worsen the PPI deficit observed in maternally deprived rats. Previous studies have reported a reduction in PPI in mice treated with a corticosterone pellet implant [16,56–58], however there appears to be no studies to date that have investigated the long-lasting effects of chronic corticosterone treatment (i.e., days/weeks following termination of the treatment) on PPI.

Likewise, chronic corticosterone treatment did not have a long-lasting effect on spatial learning ability or spatial working memory, although there was a tendency for chronic corticosterone treatment to impair acquisition of the T-maze delayed alternation task in non-deprived, but not maternally deprived rats (Fig. 3). While this tendency was not statistically significant, it is possible that a larger group size may reveal significant differences. Nevertheless, these findings are consistent with two previous studies that reported no effect of chronic (4 or 8 weeks) corticosterone treatment on spatial learning and memory performance on the Morris water-maze 2 weeks after termination of corticosterone treatment [3,29]. Given that previous studies have demonstrated impaired performance on the Morris water-

maze in rats immediately after chronic corticosterone treatment [45], our results, together with the studies mentioned above, suggest that the effect of corticosterone on spatial learning and memory performance may be reversible, at least in the adult brain, following the cessation of treatment. Indeed, previous studies suggest that stress- or corticosterone-induced functional changes reflect changes at the anatomical level [5,20,28,31] and stress-induced structural changes have been shown to be reversible within 14 days following the termination of treatment [6,54].

A limitation of the present study is that plasma corticosterone levels were not determined during the pellet implant period and therefore we cannot be certain that the pellet implant resulted in elevated levels of corticosterone in the blood. However, in a separate cohort of rats, we have previously demonstrated elevated plasma corticosterone levels during the 3-week pellet implant that approximate to that observed during exposure to moderate levels of stress [12]. Furthermore, in the present study, the corticosterone pellet implant significantly suppressed body weight gain during the 3-week implantation period (Table 1), suggestive of elevated levels of circulating corticosterone.

The timing, nature and duration of the environmental insults, as well as the opportunity for recovery between insults, is likely to dictate the nature and extent of the behavioural deficits. While stress- or corticosterone-induced structural and functional changes in the adult rat appear to be reversible, there is some evidence that chronic stress during the peri-pubertal or juvenile period (i.e., pnd 28–60) may have more enduring effects on both hippocampal structure and learning and memory processes [17]. Juvenile (pnd 28) rats exposed to 4 weeks of chronic, variable stress displayed hippocampal volumetric changes and memory impairment, 3 weeks (but not 24 h) following the cessation of the stress paradigm. These changes in hippocampal volume were thought to result from an arrest of the normal developmental growth of this region that occurs during the transition into young adulthood. It is possible that chronic exposure to corticosterone during the peri-pubertal period may have had a greater effect on the developing brain, leading to more persistent behavioural effects.

Due to a growing body of evidence that brain volume changes in schizophrenia may be progressive over the course of the illness (for a review, see [43]), the two-hit hypothesis of schizophrenia has gained increasing attention [32]. According to this model, the development of schizophrenia requires two or more adverse events or 'hits' over the life span. The first 'hit' may consist of genetic risk and/or an environmental insult during a critical period of early brain development, which renders the brain vulnerable to adverse environmental events later in life (second 'hit'), particularly during adolescence, which subsequently leads to the development of schizophrenia [2,30,34,59]. Exposure to stress has been suggested as one such risk factor that may act as a second 'hit' [34]. In the present study, we observed no interaction between neonatal maternal deprivation (an experimental paradigm known to affect early brain development) and post-pubertal chronic corticosterone treatment on adult behaviour. While maternal deprivation resulted in persistent behavioural deficits, chronic corticosterone treatment during young adulthood did not produce any further long-lasting behavioural effects. These findings possibly reflect the relative vulnerability and resiliency of the developing and adult brain, respectively.

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