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Delayed alternation performance in rats following recovery from early iron deficiency

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ABSTRACT

Early iron deficiency (ID) is one of the most common nutrient deficiencies in both developed and developing countries. This condition has been linked to perturbations in myelin formation, alterations of monoamine neurotransmitter systems particularly in the striatum, and deficits in energy metabolism particularly in the hippocampus (HP) and prefrontal cortex (PFC) in rats. Early ID has also been traced to long-term behavioral consequences in children in domains linked to these neuropathologies. The current experiment assesses formerly iron deficient (FID) adult rats on a delayed alternation (DA) task — a procedure thought to be sensitive to PFC dysfunction. Rat dams were started on an iron deficient chow at gestational day (G) 2 and maintained on this diet until postnatal day (P) 7; behavioral training began at P 65 when animals were iron replete. FID animals exhibited accelerated acquisition ($p = 0.002$) and fewer errors ($p = 0.003$) on the DA task compared to controls. These findings may reflect an imbalance between hippocampal and prefrontal modulation of this behavior most likely emanating from long-term hippocampal disinhibition by early ID that persists in spite of early iron treatment from P 7.

1. Introduction

Iron deficiency (ID) is one of the most common forms of undernutrition in the world [1–3]. Research with human and animal subjects has linked early ID to disturbances in myelination, monoamine, glutamatergic and GABAergic neurotransmitter systems, and hippocampal structure and function [1,4–19]. Early ID decreases energy metabolism within the hippocampus (HP) and prefrontal cortex (PFC) while the animal is iron deficient [4,9,12]. A consequence of this decreased metabolism is altered neuronal growth and differentiation in brain structures (i.e., HP and PFC) that are actively developing during the period of ID. Another body of work suggests early ID has significant negative effects on the dopamine system within dorsal striatum and PFC — some of which may not be reversible with iron repletion [1,2,13–15,17–24]. Conversely, inactivation of the HP can result in greater cognitive flexibility on certain tasks, particularly those dependent on nucleus acumbens integration of HP and PFC input [25,26].

Despite evidence indicative of developmental biochemical anomalies within the PFC of iron deficient animals [4,15,18,22] and studies suggestive of executive dysfunction in children after exposure to early ID [27–31], no animal behavior studies have expressly investigated this issue. The current study used a delayed alternation (DA) task – a procedure sensitive to prefrontal dysfunction [32–35] – to investigate the long-term effect of early ID on an aspect of PFC functioning. Based upon previous neurohistological investigations conducted in the iron deficient rat pup [4], we hypothesized long term deficits would be observed in the DA task — suggestive of persistent PFC dysfunction secondary to early ID. Instead, we show that this particular PFC mediated behavior is enhanced in formerly iron deficient (FID) rats compared to never iron deficient controls — suggestive of recovery of PFC while providing indirect support for long-term HP dysfunction following early ID.

2. Materials and method

All procedures were approved by the Animal Care and Use Committee of the University of Minnesota and complied with the National Institute of Health policies on animal care.

2.1. Subjects

Procedures used a total of 54 (28 iron deficient and 26 iron sufficient) Charles River Sprague-Dawley male rats derived from 10 litters.

2.2. Apparatus

The T-maze apparatus used was modified from a radial arm maze (see Fig. 1) so that only three arms were available to the animal. The stem of the resulting t-maze served as the start arm. The animals were restricted in the center of the maze by the placement of walls equal to

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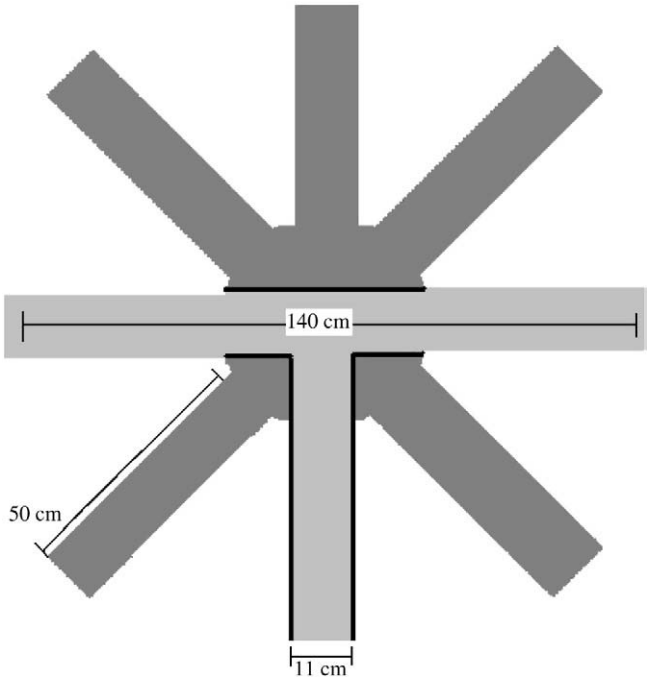

Fig. 1. Eight arm radial maze modified to form the t-maze used in the delayed alternation task.

the height of the vertical hatch door (23 cms) to form the t-maze. The walls of the maze arms were extended from a 3 cm lip to a 23 cm height equal to the height of the guillotine door. Furthermore, the maze was rotated on a daily basis so that the rat began each training day in a different spatial orientation compared to the extra maze cues. These manipulations were undertaken in order to minimize as much as possible the access to extra maze cues, which may recruit other brain regions such as the HP.

3. Procedure

A more detailed explanation of the general procedures can be found in Schmidt et al. [36]. Briefly, we obtained pregnant Charles River Sprague-Dawley dams from Charles River laboratories (Wilmington, MA) within 1–2 days of plug-positive evidence of pregnancy. At gestational day two, 4 of the 10 dams were started on an iron-sufficient diet (198 mg of elemental Fe/kg chow; Harlan Teklad; Madison, Wisconsin), and 6 of the 10 dams were started on a low-iron diet (3–6 mg of elemental Fe/kg chow; Harlan Teklad). Litters were culled to eight pups two or three days after birth, and iron deficient dams returned to a standard (iron-sufficient) diet on postnatal day (P) 7.

To ensure adequate motivation to complete behavioral testing, starting at P 56, all male animals were placed on food restriction to reduce them to 80–85% of their free-feeding body weight. The FID animals completed training at the same rate as controls (approximately 90%) and did not exhibit any increased health problems following the neonatal period.

Two consecutive days before behavioral training began, animals were presented with the reinforcer (45 mg fruit punch flavored sucrose pellets (Research Diets Inc New Brunswick NJ) in their home cage in order to familiarize them with the food reward. Also on these days, each animal was placed in the maze for 5 min a day, in order to habituate them to the apparatus and testing environment. Behavioral training of male animals (female rats were not included in this study) began at P 65.

The basic design and approach to data analysis of the DA task were derived from previous investigations [34,35,37,38]. Training began by placing the animal in the start arm. On the first trial of each day, both of the cross arms contained a food reward. After the animal obtained the reward from one of the arms it was removed from the arm and placed back into the start arm (stem of the T). After a 10 s delay, the door of the start arm was lifted and the animal was allowed to make another arm choice. However, on the second and subsequent trials, only the arm not previously baited contained a food reward. This process was repeated until the animal made eight arm entries or until 10 min elapsed. If an animal did not alternate its response on a particular trial (i.e., visited the same arm two trials in a row), it was returned to the start arm and the bait remained in the opposite arm until the animal alternated its behavior. Training continued until animals reached criterion (defined as seven of eight correct entries on two consecutive days of training). Performance was evaluated in terms of the number of days of training until animals met criterion, the number of errors animals made before reaching criterion, and the average time necessary for an animal to complete the task on the two days in which criterion performance was achieved.

4. Iron status

Iron status of sibling rats was assessed at P 7, at the peak of ID, and at P56 after complete iron repletion. Blood samples for hematocrit were taken from 7 iron deficient and iron sufficient rats at both time points, with heparinized capillary tubes from the right cardiac atrium, before the animal was perfused for brain tissue iron assessment. The tubes were spun at 3000×*g* for 20 min and measured with a standard hematocrit reader. Tissue iron concentrations were assayed in perfused whole brain samples from 5 iron deficient and iron sufficient rats at each time point as previously described [6,9]. Briefly, brains were lyophilized and digested with nitric-perchloric and measured by atomic absorptiometry. Brain iron concentrations are expressed as mcg Fe per g dry weight. Regional brain iron status in the HP and PFC was assessed by modified Perl's stain as previously described [11]. Briefly, fixed frozen 20 μm brain sections from HP and PFC in 5 iron deficient and iron sufficient rats were incubated in 10% potassium ferrocyanide for 5 min followed by incubation in a freshly made Perl's solution for 20 min. The Perl's reaction was intensified with 3,3′ diaminobenzidine (DAB). Control sections were incubated in Perls solution with PBS substituted for potassium ferrocyanide, and were negative for any DAB staining.

5. Results

The model induced significant ID at P 7 as indicated by a 53% reduction in hematocrit and a 61% reduction in brain iron concentration. The iron deficient group had less Perl's staining in the HP and PFC than the iron sufficient group at P 15. All of these deficiencies had completely resolved at P 56, prior to the onset of behavioral training (Table 1; Fig. 2a, b), consistent with previous reports with this model [6,7].

The FID animals acquired the DA procedure more rapidly than never iron deficient control animals (FID mean = 8.86 days ± 3.84 versus 11.88 days ± 3.95 for controls), Wilcoxon signed rank test (df = 1, N = 54) = 885.5, p = 0.002 $d = 1.08$) (see Fig. 3a). FID animals made fewer errors before reaching criterion than controls (FID mean = 12.25 errors ± 7.49 versus 17.46 ± 7.01 for controls), Wilcoxon signed rank test = (df = 1, N = 54) = 875.0, p = 0.003 $d = -0.8335$) (see Fig. 3b). Despite these differences, both groups took approximately the same

Table 1
Hematocrits and brain iron concentrations at P7 and P56.

	Hematocrit (%)			Brain iron (mcg/g dry weight)		
	IS	ID	p-value	IS	ID	p-value
P7	36 ± 3	17 ± 2	<0.001	48.8 ± 6.1	19.5 ± 2.9	<0.001
P56	47 ± 3	47 ± 4	0.88	40.3 ± 5.3	39.0 ± 3.4	0.65

Values are means ± SD; p-values generated from Bonferroni corrected t-tests.

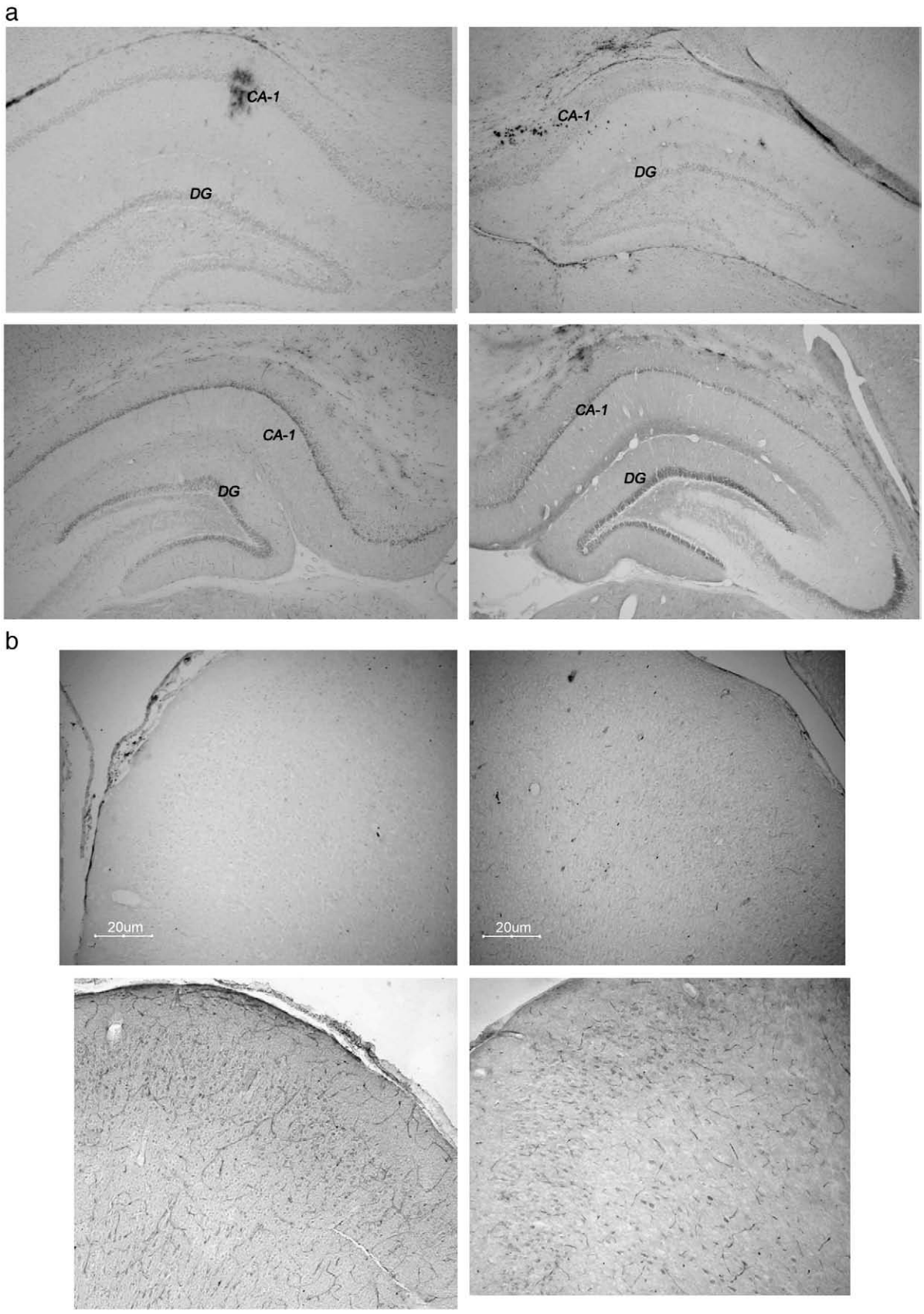

Fig. 2. a. Perl's staining of representative sections of ID (left panels) and IS (right panels) hippocampus at P15 (top row) and P56 (bottom row). CA-1: Cornu Ammon 1; DG: Dentate Gyrus. b. Perl's staining of representative sections of ID (left panels) and IS (right panels) in the prefrontal cortex at P15 (top row) and P56 (bottom row).

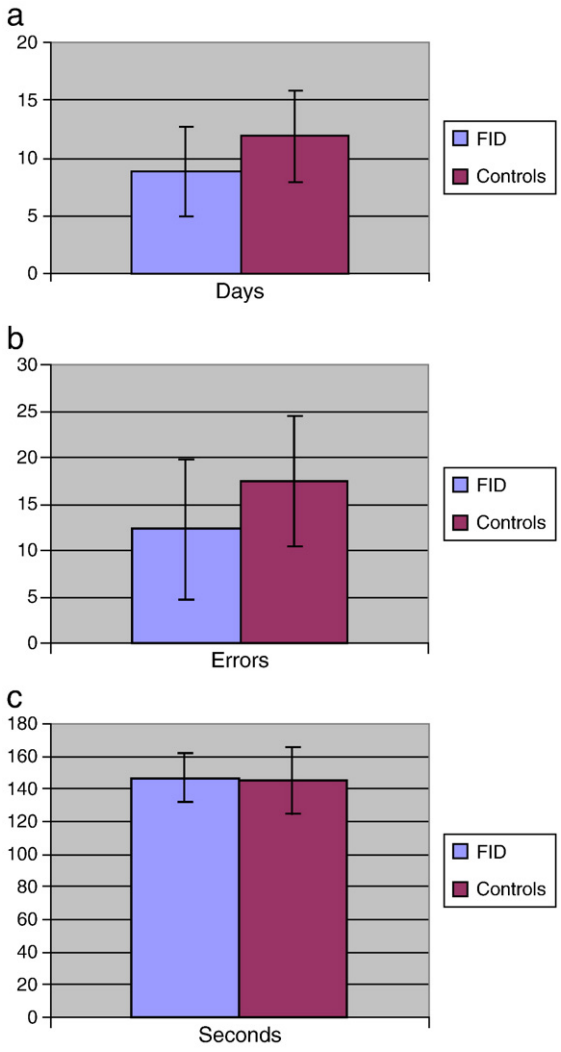

Fig. 3. a. This figure shows a bar graph of means and standard errors of days to criterion for both groups. b. This figure shows a bar graph of means and standard errors for the number of errors made prior to reaching criterion for both groups. c. This figure shows a bar graph of the mean and standard error for time in seconds to complete the maze on criterion days for both groups.

amount of time to complete the task on the criterion days (FID mean time = 146.83 s ± 14.61 versus 145.18 s ± 20.37 for controls), Wilcoxon signed rank test (1, 29) = 158.5, p = 0.394 d = 0.0081) (see Fig. 3c).

6. Discussion

These novel results indicate grossly intact and indeed paradoxically facilitated performance of FID rats within the DA task — suggestive of preserved PFC functioning. Further, the relatively strong effect sizes indicate that the findings represent more than a subtle difference between groups.

Initially, we hypothesized that performance deficits, not enhancements, due to long-term PFC alterations would be present in the FID animals on this task based on several independent lines of evidence. First, using the same animal model of fetal/neonatal ID as in the current study, de Ungria et al. [4] demonstrated that PFC aerobic metabolism is sensitive to iron status. However, they obtained their findings in young rats at P 10 while their brains were still profoundly iron deficient. The finding was not surprising since cytochrome C oxidase is an iron dependent index of neuronal energy status [39]. Reduction of its content in brain regions during ID is consistent with previous experiments illustrating profound effects of extant ID on neuronal oxidative metabolism [9,40]. However, no studies have assessed if these deficits continue into adulthood after recovery from early ID.

Given that animals were provided with an adequate iron substrate beginning at P 7, it seems plausible that the energy producing capacity of the PFC likely had recovered to control levels without residual structural deficits by early adulthood — a conjecture supported by normal Perl staining in the PFC at P 56 and by previous research indicating amelioration of early PFC injuries [41]. Nonetheless, even if frontal recovery were found to play a role, FID animals would not be expected to surpass never iron deficient controls, but rather to exhibit equivalent performance on this task. Thus, the "recovery of function" hypothesis does not appear adequate to explain the current results.

Second, the original studies by Youdim and colleagues [14–17,19] that demonstrated changes in the dopamine system and suggested possible alterations in prefrontal dopamine [15] and the subsequent follow-up investigations by Beard et al. [2,20] that demonstrated changes in prefrontal dopamine metabolism concerned mainly postnatally induced ID. Because the PFC is a later developing structure relative to the HP, it may be more vulnerable to postnatal insults than to pre or perinatal insults. Additionally, the dietary manipulation itself may have contributed to the current findings. That is, the current protocol induced a significant level of ID (upwards of 40% brain iron loss) [4,9,12]. Thus, other dietary protocols that used different amounts of iron deficient ciao [1,2,14,15,19–21] may have resulted in a different pattern of behavioral findings. Finally, the findings of Lozoff and colleagues [27] showing long-term deficits in executive functions in adolescents who had been iron deficient as young children were collected in a population that experienced longer-term postnatal ID. We speculate that the different timing, dose, and duration of exposure in these various investigations of early ID account for the discrepant results between previous research and the current study.

A consideration of the cooperative and competitive interactions of HP, PFC and striatum in goal oriented behavior may provide a potential explanation of our findings [25,26]. Specifically, interactions of prefrontal cortical and limbic inputs on the nucleus accumbens and their modulation by mesolimbic dopamine D1 and D2 receptors respectively modulate the tonic and phasic release of dopamine from striatal neurons and seem to be of primary importance in facilitating goal-oriented behaviors [25]. As such, disruption of D2 receptor activity results in enhancements of behaviors supported by the PFC and impairment of behaviors heavily supported by HP [25]. Given that hippocampal function [5,6,36,42] and striatal D2 receptors [20–22] are both impaired in FID rats [15,18,19] it is plausible that these factors act together to facilitate performance of tasks that are primarily dependent on the PFC as demonstrated in the current study.

The tendency of healthy adult rats to initially employ a spatial (i.e., hippocampal) learning strategy in a novel learning situation [43,44] may also contribute to the findings. Work by Devan and White [43] indicates that rats display an initial preference to use hippocampal dependant spatial learning when both spatial and cue-based information are available. Additionally, Packard and McGaugh [44] found animals trained in a t-maze initially employ a hippocampal dependant spatial or "place" strategy to solve the task before shifting to a striatally dependant cue-based or "response" strategy.

The DA task under certain conditions activates the HP [45–47]. Attempting to use this approach would be unproductive in the current experiment because precautions were taken in the design of the study to reduce spatial map formation by limiting access to extra-maze cues thereby minimizing hippocampal influence. Nonetheless, we hypothesize that control animals initially attempted to solve the DA procedure via an inefficient and unproductive hippocampal mediated spatial learning strategy, and failing this, switched to the "correct" PFC mediated approach. Since gestational ID affects long-term hippocampal structure, physiology, and function [5,6,36,42], we speculate that FID animals did not attempt the "non-productive" hippocampal mediated spatial learning approach and adopted the PFC approach sooner.

These results are not without precedent as there is evidence suggesting that hippocampal lesions can enhance some types of learning [48]. Walker, Messer, Freund, & Means [49] trained control rats and rats with hippocampal and cortical lesions to perform a go, no-go task in which bar presses were rewarded on alternating trials. They varied the inter-trial-interval (ITI) and found that hippocampal lesioned animals outperformed controls and cortical lesioned groups at the shortest (10 s) ITI.

Another example involves context conditioning, a different type of hippocampally mediated behavior [50]. Cheung and Cardinal [48] demonstrated that animals with hippocampal lesions acquired an instrumental learning task more rapidly than controls when brief (several seconds) delays were interposed between the response and presentation of the reward. They hypothesized that interfering contextual information retarded acquisition of action-outcome contingencies within controls. However, by decreasing the salience of contextual information, they argued that hippocampal lesions resulted in accelerated pairing of the stimulus with the presentation of the reward. In the current study, control animals may have initially associated the maze context with the presentation of the food reward, thus delaying their acquisition of the task. Conversely, FID animals experienced little to no contextual interference and thus acquired the rule governing reinforcement more rapidly.

The current investigation and interpretation have several potential limitations. For example, measures of dopamine concentration and/or neural activity within the striatum or PFC and the addition of a HP lesion group would have been potentially helpful in further explicating our results, but were beyond the scope of the current study. Nevertheless, these would make excellent areas for future investigations, and would provide additional evidence of hippocampal dysfunction following fetal/neonatal ID. Moreover, it is possible disruptions in dopamine modulation and/or the hypothesized lack of hippocampal competition are suppressing "real" disruptions of PFC function observable in other procedures.

This study provides a novel finding indicating that, despite early changes in PFC metabolism, FID adult animals exhibit facilitation of a task considered to recruit prefrontal structures. To our knowledge, this investigation is one of the first to examine directly the performance of adult animals following fetal/neonatal ID with respect to this type of learning, and is the only study to demonstrate significantly better performance by FID animals compared to controls on any kind of learning procedure. Although this experiment suggests early ID in rats (specifically, ID occurring in the fetal/neonatal period) does not adversely impact performance on the DA task, these findings provide some indirect support for the hypotheses that ID occurring within the fetal and neonatal period results in long-term alterations in the monoamine system and/or attenuated hippocampal function. Moreover, the present results provide strong evidence that early ID can permanently perturb the relationship between neural systems involved in learning and memory; thereby altering how these animals acquire information and interact with their environment.

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