EFFECTS OF EARLY LIFE EXPERIENCES ON BRAIN STRUCTURE AND FUNCTION: NEUROGENESIS & DECISION MAKING

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Background

- During **early life**, brain structures involved in cognitive processing are still developing.
- Exposure to stress during perinatal life can enhance **stress** responsiveness and lead to increased vulnerability for psychiatric disorders later in life.
- In animal models of early life stress, we can study the biological basis of stress-induced structural and behavioral alterations that may contribute to an enhanced risk for **psychopathologies** later in life.
- **Maternal deprivation** (MD) is a well established animal model for early life stress. MD leads to increased levels of corticosterone and disrupts the stress hyporesponsive period.
- Early life stress affects both neurogenesis and hippocampal plasticity.
- This is thought to be mediated by **glucocorticoid** receptors, which can be blocked by mifepristone (see previous results below).

Aim

- **Investigate the effects of a brief period of MD on brain structure and function during adolescence and adulthood**.
- We wanted to address the following questions:

1) The effects of MD on neurogenesis at postnatal day 29 (females).
2) The effects of MD on decision-making processes in young-adult male rats.
3) The effects of glucocorticoid receptor blockade (mifepristone administered during postnatal day 26-28) on both the structural and behavioral alterations induced by MD.

Methods

- We used Wistar rats.
- Animals were exposed to 24 h maternal deprivation at postnatal day (PND) 3.
- From PND21 onwards, pups were group-housed in pairs by gender and treatment group.
- From PND 26-28 half of the maternally deprived and control groups received either mifepristone or vehicle, administered through an oral syringe directly into the stomach.

Experiment 1

At PND29 the females were sacrificed and perfused. The number of young, differentiating neurons were identified with an antibody against the microtubule-associated protein doublecortin (DCX; ongoing experiments, not shown).

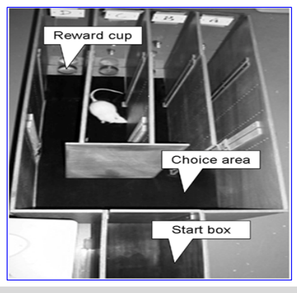
Immunohistochemistry for Ki-67 was used to assess cell proliferation.

Experiment 2

To assess the functional effects of maternal deprivation, 12 week old male rats performed the Rodent Iowa Gambling Task (r-IGT).

To study the neural substrates underlying decision-making, we measured expression of the immediate early gene c-fos in the medial prefrontal cortex directly after the task..

r- IGT



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Results

Experiment 1

BODY WEIGHT

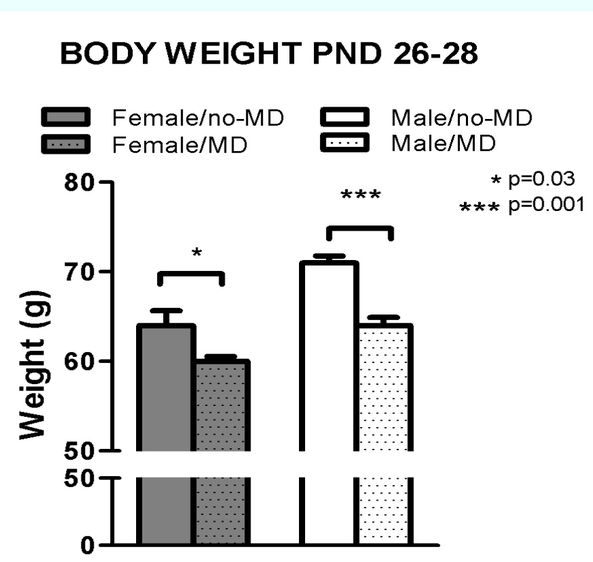


Fig. 1 | Averaged body weight in the maternally deprived groups (females and males) is reduced. Error bars indicate SEM.

CELL PROLIFERATION

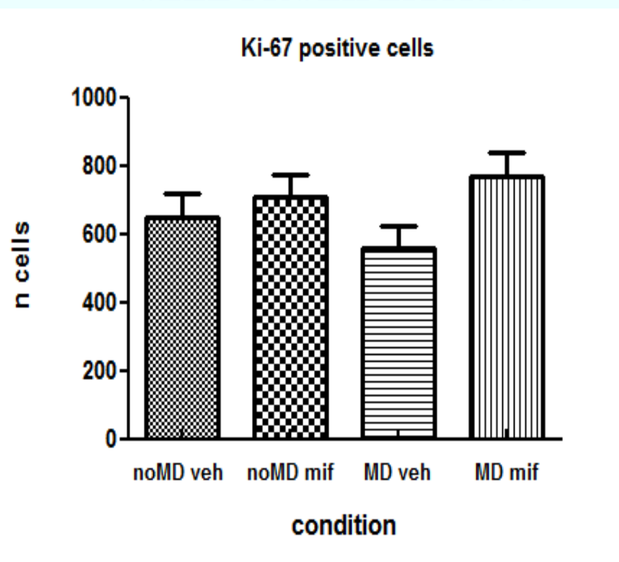


Fig. 2 |Mean number (+ SEM) of Ki-67 positive cells in hippocampal hilus per 10 sections. We observed no differences between the groups.

Experiment 2

rIGT ADVANTAGEOUS ARM VISITS

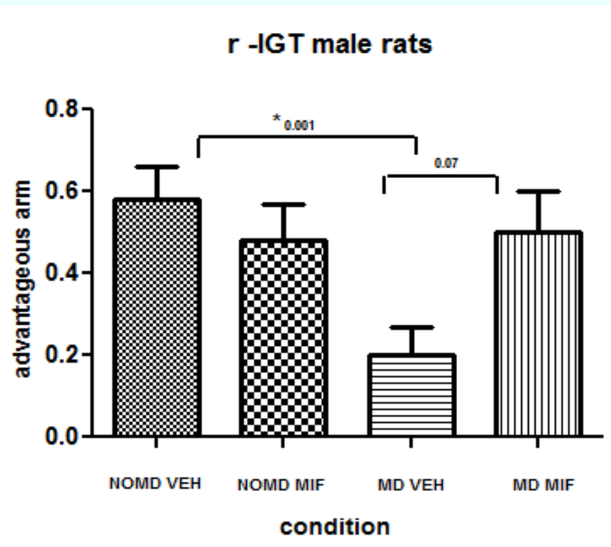


Fig. 3 | MD male rats showed a lower fraction of visits to the advantageous arm, compared to control animals. This was prevented by mifepristone treatment at PN 26-28.

rIGT EMPTY ARMS VISITS

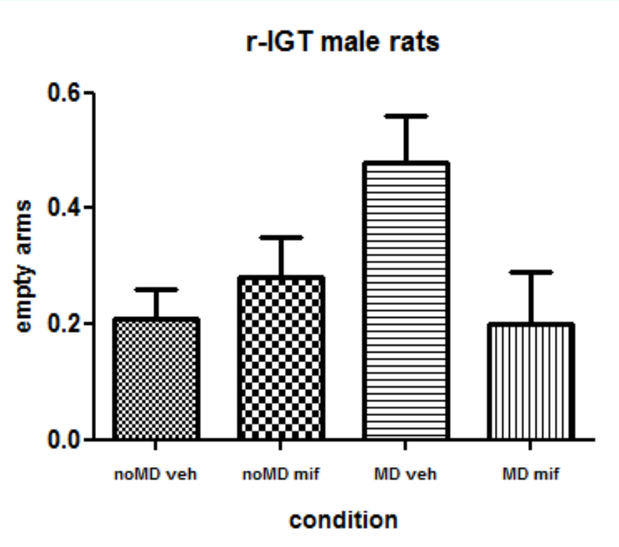


Fig. 4 | MD rats had a tendency (ANOVA=0.08) to make visit empty arms more often than controls. Mifepristone treatment at PND 26-28 normalized this.

c-Fos IMMUNOHISTOCHEMISTRY

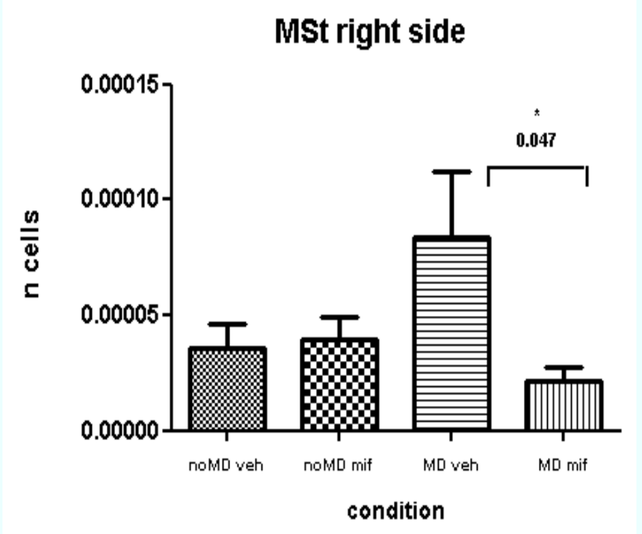
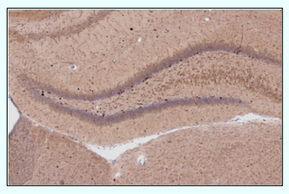


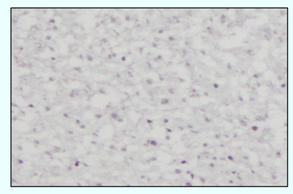
Fig. 5 | Levels of c-fos expression (number of positive cells per mm²) in the dorsomedial striatum. The number of c-fos+ cells was increased in MD compared to controls rats. This was reversed by mifepristone treatment at PND 26-28.
* p< 0.05 as revealed by Bonferroni testing.

PICTURES OF STAINING

KI-67



c-Fos



Conclusions

- Male and female maternally deprived rats had lower body weights at PND26 compared to the non-deprived groups.
- At PND29, maternally deprived female rats showed a trend towards a lower number of Ki-67 positive cells in the hippocampal hilus, compared to controls. Treatment with mifepristone resulted in a comparable number of Ki+ cells as in controls.
- Male MD rats had a tendency to avoid empty arms and had a significantly low fraction of visits to the advantageous arm compared to non-deprived rats, when tested in a rIGT at 3 months of age.
  This deficit was fully reversed by mifepristone treatment at PND 26-28.

→ These preliminary data support that treatment with mifepristone in adolescence can lastingly reverse adverse effects of early life stress.