

Consequences of *in utero* methamphetamine exposure on behaviour in the adult rat

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Introduction

Methamphetamine (MA) is widely abused amongst females of child-bearing age, with an approximate 1.5% prevalence of use during pregnancy^[1]. MA can cross both the placenta^[2,3] and the foetal blood-brain barrier and so *in utero* exposure may lead to behavioural deficits later in life^[4,5]. Controlled longitudinal studies on the behavioural effects of prenatal exposure to MA in humans are not feasible, for ethical and logistical reasons. Animal alternatives are a useful way of assessing behaviours which are also seen in humans. The purpose of this study was to determine the effects of *in utero* MA exposure on behaviour in the adult rat.

Methods

Pregnant females orally dosed from day 7-21 of gestation

Vehicle (distilled water, n=8)

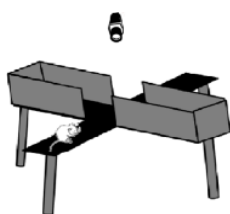
MA (5mg/kg, n=8)

Male and female offspring tested during adulthood
(from 8-11 weeks old, n=8/group)

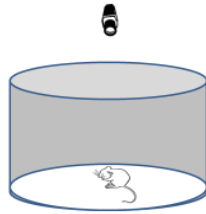
Tests scored manually (Forced Swim Test) or with Ethovision® XT tracking software. Data analysed using Two-Way or Repeated Measures ANOVAs with relevant Post-Hoc tests. All data in graphs are expressed as mean + SD

Apparatus used

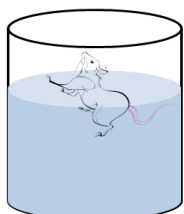
A: Elevated Plus Maze
(Percentage time spent on open arms- Anxiety)



B: Open Field
(Distance moved and velocity- Locomotor Activity)



C: Forced Swim Test
(Immobility time- Behavioural Despair)



D: Morris Water Maze
(Time and distance to find platform- Spatial Learning & Memory)

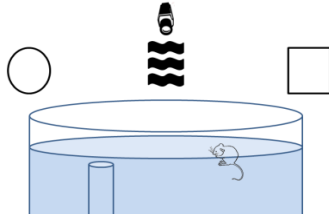


Figure 1 A-D: Behavioural tests carried out on adult animals exposed *in utero* to either vehicle or MA.

Results

***In utero* MA exposure had no effect on percentage open arm time in the Elevated Plus Maze**

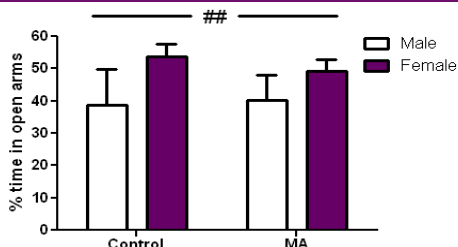


Figure 2: Results of percentage open arm times in the Elevated Plus Maze. No effect of MA was found. An overall sex difference was seen, with females having higher locomotor activity than males (## indicates this sex difference at $p \leq 0.01$).

***In utero* MA exposure leads to increased locomotor activity in adult males in the Open Field**

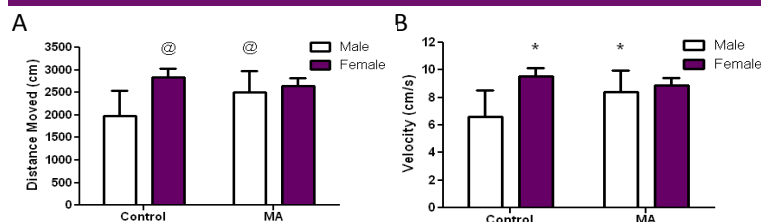


Figure 3: Results of locomotor activity in the Open Field. * indicates a significant difference at $p < 0.05$, @ indicates a trend towards a difference which did not reach statistical significance ($p = 0.056$), both when compared with male controls.

***In utero* MA exposure leads to increased immobility time in adult females in the Forced Swim Test**

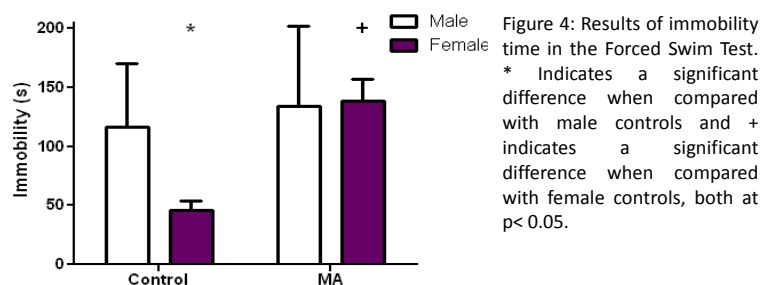


Figure 4: Results of immobility time in the Forced Swim Test. * Indicates a significant difference when compared with male controls and + indicates a significant difference when compared with female controls, both at $p < 0.05$.

***In utero* MA exposure had no effect on time to find platform, path length or swim speed in the Morris Water Maze**

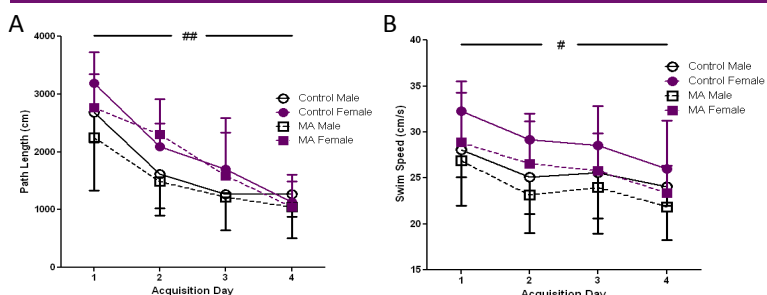


Figure 5: Results of A: Path length and B: Swim speed in the Morris Water Maze. Overall sex differences were apparent for both parameters (males had shorter path length and females swam faster). # and ## indicate overall sex differences at $p < 0.05$ and 0.01 respectively. Results for time taken to find platform showed a similar pattern to path length results.

Conclusion

In conclusion, sex differences were evident in all tests carried out in the present study. There was a differential effect of *in utero* exposure to MA, with effects seen in the Open Field and Forced Swim Test, but not the Elevated Plus Maze or Morris Water Maze. These effects came in the form of sex-specific alterations, consisting of a loss of sex differences seen in control animals in these tests. The outcomes of this study highlight the importance of including both sexes and employing an extensive battery of tests in studies investigating the behavioural consequences of *in utero* exposure to MA. As males and females differ not only hormonally, but also in monoamine levels^[6] and monoamine oxidase activity^[7], post-mortem investigations will be conducted to determine the mechanisms by which these sex-specific alterations may be caused.

References

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