A novel double-hit animal model of schizophrenia: behavioural assessment in male and female mice

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Background: A growing body of evidence support that maternal prenatal infections represent a risk factor for schizophrenia in offspring [1]. Moreover, stressful events during critical neurodevelopmental periods, such as adolescence, may trigger the onset of the disease in predisposed individuals [2]. Thus, a prenatal priming event (i.e. maternal infection during pregnancy) that would induce vulnerability, followed by a second stressful hit in peripuberty may lead to the onset of schizophrenia [3].
Aim: We aimed to develop and characterise a novel double- hit animal model of schizophrenia in male and female CD1 mice, based on prenatal maternal immune activation (MIA) followed by social isolation (SI) in the peripubertal period.

Methods: Polyriboinosinic:polyribocytidilic acid [Poly (I:C)] (7.5 mg/kg i.p.) or saline (5 ml/kg i.p.) was administered to pregnant dams at gestational day 9.5. At post-weaning (postnatal day 21), offspring were either housed in groups (4 animals per cage) or isolated during at least 8 weeks until behavioural assessment. The four experimental arms generated (MIA, SI, MIA+SI and control) in both, male (n = 12/arm) and female (n = 12/arm) mice, were tested for social behaviour—Social Preference Test (SPT)—and cognitive status—Novel Object Recognition Test (NORT) and Y-Maze Spontaneous Alternation Test (YMSAT)—. Additionally, in a subsample of mice (n = 6/sex/arm), locomotor response to acute amphetamine administration (5 mg/kg i.p.) was evaluated during a 120-minute period. Data were analysed using non-repeated or repeated measures three-way ANOVAs as appropriate.

Results: In the SPT, social exploration time was significantly reduced by MIA ($F[1,82] = 9.48$; $p<0.01$) and SI ($F[1,82] = 7.92$; $p<0.01$). Non-social exploration was not affected by any of the two hits (MIA: $F[1,82] = 0.10$; $p = 0.75$; SI: $F[1,82] = 0.44$; $p = 0.51$). A significant effect of sex on both social ($F[1,82] = 19.69$; $p<0.001$) and non-social ($F[1,82] = 11.89$; $p<0.001$) exploration time was found, with higher exploration times in males than in females. The NORT discrimination index (DI) was significantly impaired by MIA ($F[1,85] = 10.93$; $p<0.001$) and SI ($F[1,85] = 7.46$; $p<0.01$). DI scores were significantly influenced by sex ($F[1,85] = 17.27$; $p<0.001$), being higher in females than in males. Of note, both male and female double-hit groups (MIA+SI) showed worse scores in SPT and NORT compared to single-hit groups. Spontaneous alternation in the YMSAT was not affected by any of the hits or sex (MIA: $F[1,88] = 0.67$; $p = 0.42$; SI: $F[1,88] = 1.28$; $p = 0.26$; sex: $F[1,88] = 2.52$; $p = 0.12$). No

significant “sex x hit”, “hit x hit” or “sex x hit x hit” interactions were found in neither SPT, NORT nor YM-SAT. A time dependent locomotor response to amphetamine was found in all male ($F[3.05, 60.92] = 6.49$; $p<0.001$) and female ($F[2.41, 45.82] = 10.88$; $p<0.001$) experimental groups. The hyperlocomotion induced by amphetamine was significantly increased by SI in female ($F[1,19] = 5.36$; $p<0.05$) but not in male ($F[1,20] = 0.82$; $p = 0.38$) mice. No significant “time x hit”, “hit x hit” or “time x hit x hit” interactions were found in locomotor response to amphetamine.

Conclusion: These results showed a significant impact induced by MIA and SI on schizophrenia related behaviours at adulthood in both sexes. These data support the double-hit model as a valuable translational tool in schizophrenia research.

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References

[1] Brown, A.S., Meyer, U., 2018. Maternal Immune Activation and Neuropsychiatric Illness: A Translational Research Perspective. Am. J. Psychiatry 175 (11), 1073–1083.
[2] Meyer, H.C., Lee, F.S., 2019. Translating Developmental Neu- roscience to Understand Risk for Psychiatric Disorders. Am. J. Psychiatry 176 (3), 179–185.
[3] Debost, J.P., Larsen, J.T., Munk-Olsen, T., Mortensen, P.B., Meyer, U., Petersen, L., 2017. Joint Effects of Exposure to Prenatal Infection and Peripubertal Psychological Trauma in Schizophrenia. Schizophr. Bull. 43 (1), 171–179.

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