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Building a framework to optimize animal models of maternal immune activation: like your ongoing home improvements, it's a work in progress

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Animal models of maternal immune activation (mIA) have emerged as both translationally relevant and essential for targeting the molecular mechanisms underlying neuropsychiatric disorders. Importantly, experimental outcomes associated with mIA vary as a function of specific study components (e.g. immunogen, dose, species/strain) and other husbandry considerations that are typically under reported yet influential to the immune response and the integrity of our animal models (Estes and McAllister, 2016; Kentner et al., 2018). In this issue of *Brain, Behavior, and Immunity*, Murray et al (2018) lay groundwork to guide the establishment of best practices for the validation and reporting of our mIA models. These steps built the foundation from which their laboratory explored the early developmental trajectory of morphometric markers in male and female offspring, revealing sexually dimorphic phenotypic changes following mIA.

Across the past decade there has been a growing consciousness calling for increased scientific rigor and reproducibility (Collins & Tabak, 2014), and for better reporting standards (Kilkenny et al., 2010) in biomedical research. Within this context, Murray et al (2018) astutely identified issues in the mIA literature including a lack of defined criteria for how important elements of our study protocols are selected. For example, the immunogens and doses of interest, administration routes and schedules, in addition to the specific strains and sex employed. While this list is not exhaustive, these are fundamental components to every mIA study and the rationale for our choices ought to be transparent and evidence-based. The importance of this is highlighted by Murray and colleagues (2018) who point out that while mice are most commonly used in the mIA literature, the use of rats is increasing too. Although some mIA mouse models have been validated, the same methods may not be appropriate for other species and further validation of these models are necessary.

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Beyond the issue of species comparisons, basic husbandry differences between laboratories (e.g. ventilation systems) may lead to large variations in the efficacy of mIA models to induce long-term programming effects (Mueller et al., 2018). Each laboratory must now take an initiative to parse out and validate the appropriate conditions under which they effectively induce their mIA models, and duly report (Kentner et al., 2018). As an excellent template of how to go about this, Murray et al (2018) evaluated the pharmacodynamic properties of the peripheral immune response, as activated by polyribonucleosinicpolyribocytidylic acid (poly I:C), in three strains of female rats. The investigators focused on plasma interleukin (IL)-6 concentration and body temperature to confirm a mIA response. The optimal dosing schedule and animal strain were then selected based on a predefined set of criteria for identifying what best worked under their particular laboratory conditions. In this case, the choice was rationalized based on the variability of the mIA response between strains and doses. Moreover, these preliminary data were reported as evidence for the methodology chosen.

Although it may have been preferable to validate the administration schedule with pregnant dams, the investigators used virgin females in order to comply with regulatory constraints such as the principles of the 3Rs (<https://www.nc3rs.org.uk/>; making considerations for both dam and fetal loss). This underscores the reality that establishing validation guidelines will be an evolving process requiring a balance between good research design, current ethical guidelines, and other laboratory limits (e.g. funding).

In addition to defining the appropriate poly I:C schedule, Murray et al (2018) verified mIA in all experimental dams via peripheral blood sampling, an accepted method for validating immunogen efficacy (Kentner et al., 2018) that, like other methods, is either underused or underreported. Murray et al.'s current work (2018) contributes to a newly growing and important trend in the mIA literature to improve the rigor and reproducibility of these models. One recent initiative is the introduction of a 'fillable' reporting checklist https://static-content.springer.com/esm/art%3A10.1038%2Fs41386-018-0185-7/MediaObjects/41386_2018_185_MOESM1_ESM.pdf; Kentner et al., 2018) that authors can complete and include as supplementary material accompanying their manuscripts. In the past we have been a disappointment in terms of adhering to such reporting initiatives, despite endorsing them (Leung et al., 2018). Hopefully the existence of an easier fillable form will improve the utilization of these systematic lists and reporting methods overall.

Since optimizing a mIA model in their laboratory, the authors are now primed to continue their long-term research goal of analyzing sex-differences in the developmental trajectory of mIA exposed offspring, beginning with fetal development and spanning across the lifespan. In the present study, Murray et al. (2018) first focus on the placenta and early fetal period. With this approach, the investigators demonstrated that poly I:C challenge on gestational day (GD)15 led to a decline in placental weights on GD21. These results are in line with observations that low placental weight is correlated with a higher susceptibility for neurological disorders, such as schizophrenia (Wahlbeck et al., 2001). Interestingly, the GD15 challenge was associated with reductions in placental: fetal brain weight ratios, yet changes in fetal brain weight (an index of fetal brain growth) were spared. This suggests that while maternal infection may cause metabolic detriments and morphometrically disrupt

offspring development, some adaptations in placental functioning may occur. Moving from the fetal period, Murray et al (2018) also analyzed microglia in the hippocampus of juvenile GD15 challenged offspring, finding an increased number of activated microglial cells in the brains of male rats. Moreover, the investigators showed a sexually dimorphic effect of pup body weight on postnatal day 21, where male poly I:C animals weighed less than saline controls.

Animal models of mIA serve as a foundational blueprint for understanding links between maternal infection and central nervous system disorders in offspring. Clearly, investigators in this field are recognizing the need to improve rigor and reproducibility in these models. Importantly, some like Murray et al (2018) are engaged in active initiatives to meet this goal. Here, they demonstrate that it is feasible to validate mIA models within our individual laboratories, and fully report the conditions of their success. Going forward, using evidence-based animal models, we may better map the developmental trajectory of the relationship between maternal infections and neurodevelopmental disorders.

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