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Title: Pilot Study of the Effects of Acute Prenatal Hypoxic Insult on Perseveration and White Matter Development in Mice

Background: Preterm and term hypoxic ischemic encephalopathy (HIE) due to perinatal global oxygen deprivation is a leading cause of neurocognitive dysfunction. White matter injury (WMI) is a frequent long term consequence of HIE; extent of WMI is correlated to severity of abnormal neurodevelopmental outcome. In particular, WMI has been associated with increased perseverative behaviors. We have developed a model of global prenatal hypoxic insult to the fetal brain to recapitulate human HIE. We hypothesize mice exposed to prenatal hypoxic insult will have increased perseverative behavior and demonstrate WMI.

Objective: To determine if adult mice exposed to prenatal hypoxic insult have an increase in perseverative behaviors and if this is correlated to abnormal white matter organization.

Design/Methods: Pregnant dams are placed in a Biospherix hypoxia chamber at E17.5. Chamber was left at 21% FiO_2 for 8 hours for normoxic condition. For prenatal hypoxic insult, the fraction of inspired oxygen (FiO_2) was titrated from 21% to 5% FiO_2 over 30 minutes and the mouse remained in the chamber for 4 or 8 hours. Pregnant mice were removed from hypoxia and allowed to give birth. Survival and weight of mice were measured. Morris water maze (MWM) was done over 8 days to assess for learning and memory in adult mice (3-4 months old) from prenatal exposures. Animals were tracked for time to platform in learning trials and time spent in platform quadrant for memory trials. *Ex vivo* MRI was performed on adult mice for diffusion tensor imaging (DTI) sequences. Eriochrome Cyanine (EC) staining for white matter was performed on adult mice and quantified with Image J.

Results: There was no difference in survival or weight of mice after prenatal hypoxia. In MWM, there was no difference in learning rate, but hypoxic males spent more time in the platform quadrant during memory testing. Subanalysis of this data indicated this was because hypoxic males were more likely to remain in the platform for the whole trial than other control or experimental mice, indicating increased perseveration in these animals. Preliminary data suggests there are differences in white matter structure and organization by both DTI and EC analysis.

Conclusions: This is a viable model to study long term effects of prenatal hypoxia. Hypoxic males demonstrate signs of increased perseveration. This is possibly correlated to WMI. Future studies will be done to confirm these findings and to studdy the effect of prenatal hypoxia on oligodendrocytes responsible for white matter formation and maintenance.