NEONATAL REPEATED SUCROSE EXPOSURE INDUCES WIDESPREAD REDUCTION OF GREY AND WHITE MATTER VOLUMES IN MICE

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INTRODUCTION / AIM
Sucrose is standard care for pain relief for minor procedures on preterm infants in the NICU. Clinical equipoise no longer exists for a randomized controlled trial of sucrose in human infants. No human or animal studies of effects of early repeated sucrose exposure on long-term brain development have been done in the context of pain.

Aim: To examine the effects of repeated neonatal sucrose treatment before an intervention on long-term brain development in mice.

METHODS
Neonatal C57Bl/6J mice (N=109, 46% male) were randomly assigned to one of 2 treatments (sucrose vs water) and one of 3 interventions (needle-prick, touch, handling). Mice received 10 interventions over a 12h period (daytime) daily from postnatal day 1 to 6 (P1-P6). A single dose of 24% sucrose (0.1-0.2mg of sucrose/g weight) or water was given orally 2 min before each intervention. At P85-95, mice were anesthetized and intracardially perfused with 4% paraformaldehyde (PFA) containing 2mM ProHance. The brains and remaining skull structures were scanned using a multi-channel 7.0 Tesla MRI. Sixteen custom-built solenoid coils were used to image the brains in parallel. Volumes of 159 independent brain regions were obtained using advanced registration methods with a pre-existing classified atlas. ANOVA was used to assess group differences, and false discovery rate (FDR<12%) to correct for multiple comparisons.

RESULTS
After correcting for total brain volume, mice that had sucrose compared to water had reduced white matter volume in the corpus callosum, stria terminalis, and fimbria (p<0.005). Cortical and subcortical grey matter was also affected by sucrose with reduced volumes of hippocampus and primary visual cortex (p<0.004). These significant changes in adult brain were found irrespective of the type of intervention in the neonatal period.

DISCUSSION / CONCLUSIONS
In a mouse pain model that closely mimics daily NICU care, early repetitive exposure to sucrose before needle-prick, touch or handling induced significant reductions in specific regional white and grey matter in adult mice. Evidence of long-term adverse effects of repetitive sucrose exposure during the neonatal period of rapid brain development is a concern.
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