

Intervention after Neonatal
Brain Injury:
Experimental Evidence

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Immature Animal Models of Cerebral Palsy

- Pre- or postnatal hypoxia-ischemia (HI) models
- With functional outcome
 - Rabbits (global injury)
 - Rats and mice (unilateral injury)
- Without functional outcome
 - Fetal lambs
 - Piglets

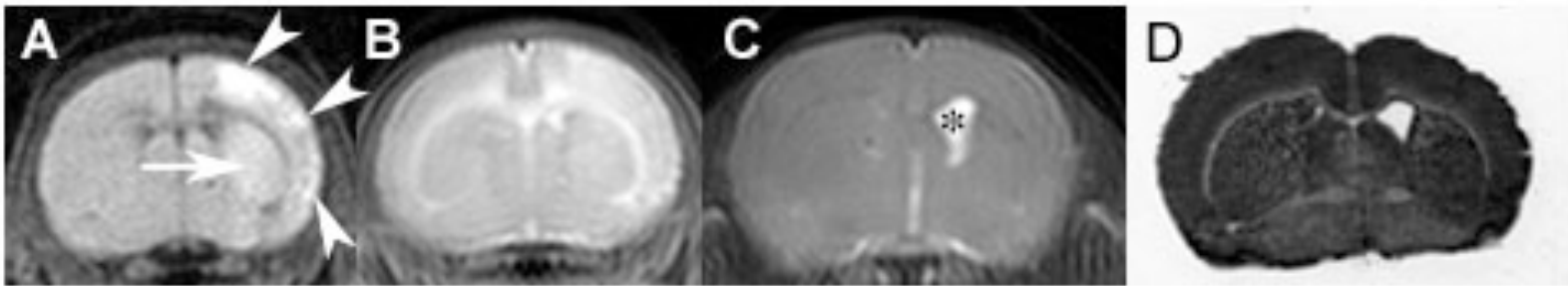
Neonatal HI Models with Functional Outcome (1)

- Rabbit: in-utero transient (40 min) aortic occlusion (upstream of uterine arteries) on E22 (70% gestation; term=31.5 d) or E29 (79% gestation)
 - Tan, Derrick, *et al.* (Evanston-Northwestern)
 - White matter injury in corpus callosum, internal capsule, corona radiata
 - Neonatal spasticity or motor deficits in ~70% of survivors, variable severity; need intensive care
 - No long term outcome; no “cognitive” measures (yet)

Neonatal HI Models with Functional Outcome (2)

- Rat - postnatal day 7 unilateral carotid ligation + timed hypoxia exposure (Rice, Vannucci and many others)
 - P7 brain similar to third trimester human
 - Cortical, striatal and hippocampal damage
 - Contralateral sensorimotor deficits, not spastic, detectable in “infancy”
 - Cognitive deficits (spatial learning and memory) detectable in juvenile, adult

P7 Rat HI: MRI and Pathology



A; Diffusion weighted imaging, striatal level P8

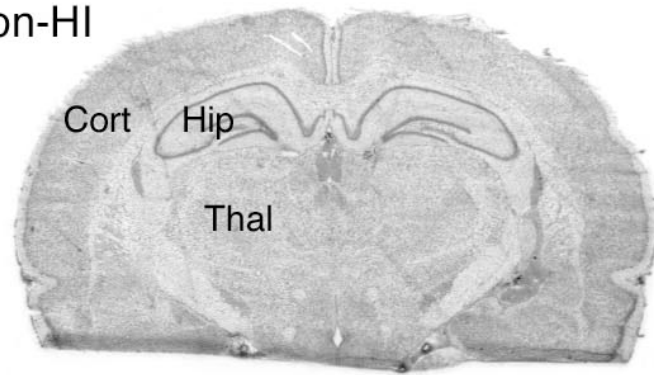
B: T2-weighted imaging, P8

C: T2-weighted imaging, P22

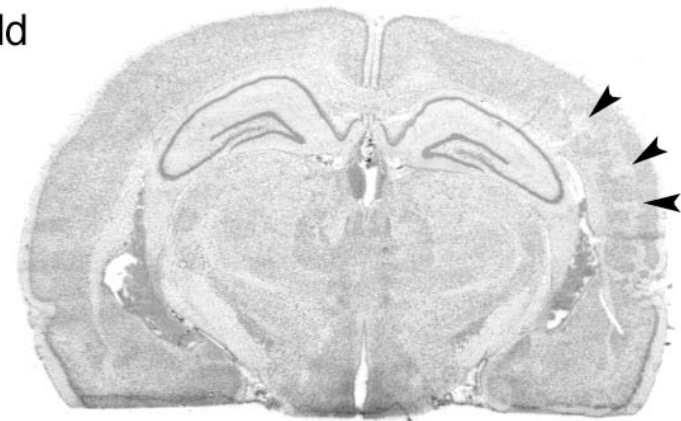
D: Nissl stained section, adult

P7 Rat HI: Range of Pathology

Non-HI



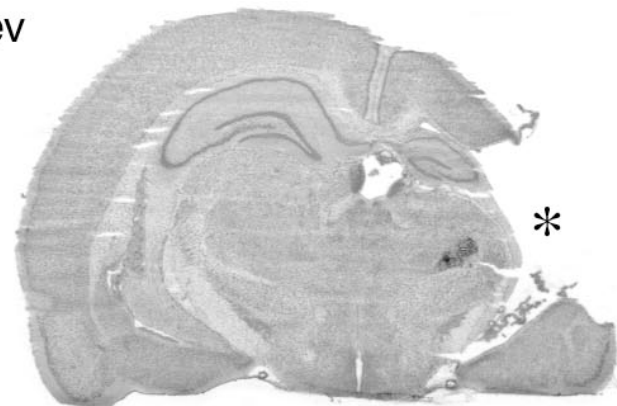
Mild



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Modeling Behavioral Intervention

- Early Neonatal Handling (Seymour Levine, Michael Meaney)
 - Increased maternal care-giving pre-weaning
 - Improved stress axis feedback regulation
 - Improved learning and memory in aging
- When applied after P7 rat hypoxia-ischemia, post-HI handling reverses post-HI learning deficits (Chou et al., 2001)
 - No effect on swim speed

Modeling Motor Intervention

- Why?
 - Understand mechanisms
 - Support more human trials
- Current modeling projects:
 - Constraint induced movement therapy
 - Treadmill training

Targeted Motor Intervention

- Constraint-induced movement therapy
 - (Early) forced use of impaired limb
- Commonly used in adult stroke victims with hemiplegia
- 3 randomized trials in hemiplegic CP (n=94)
 - 1 with significant effect
 - still “experimental” (Cochrane Database, 2007)
- Mechanism of effect unknown
- Can we model this in neonatal animals, to investigate mechanisms?

Targeted Motor Stimulation

- Unilateral (right) HI, P7 rats (1.5 h or 2 h)
- Repetitive stimulation of left vibrissae, twice daily, x 5 wks
- 2 Control groups: “Vestibular”; “testing only”
- 1^o Outcome: Weekly testing: Forepaw placing response P14-63
- 2^o Outcome: Adult testing: Rotarod (gait); Vertical Cylinder (forepaw preference); Watermaze (spatial learning)

Summary

- Forced use paradigm targeting affected forelimb accelerated recovery of reflex forepaw placing in that limb.
- Other effects: coordinated forepaw use in cylinder restored to normal
- Benefit not confounded by difference in baseline severity of injury, nor by difference in injury progression (MRI)