

# **Critical Review of Animal Models for MRI studies of Hydrocephalus**

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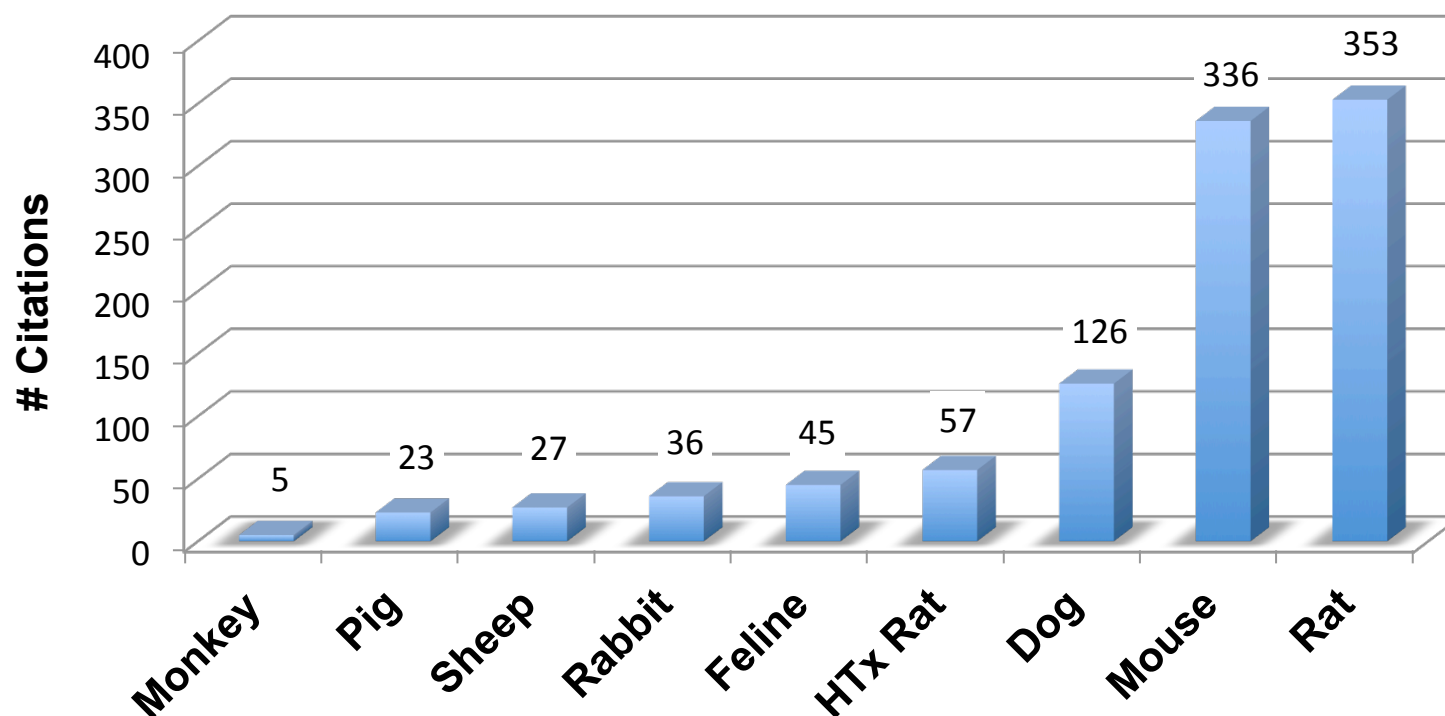
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Medical Center, Cincinnati, OH**

# Goals

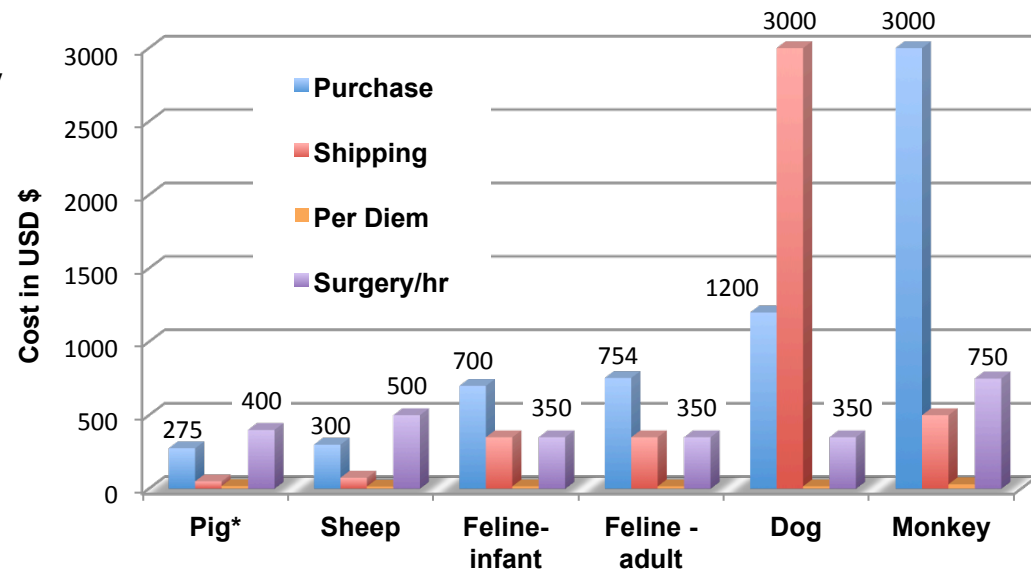
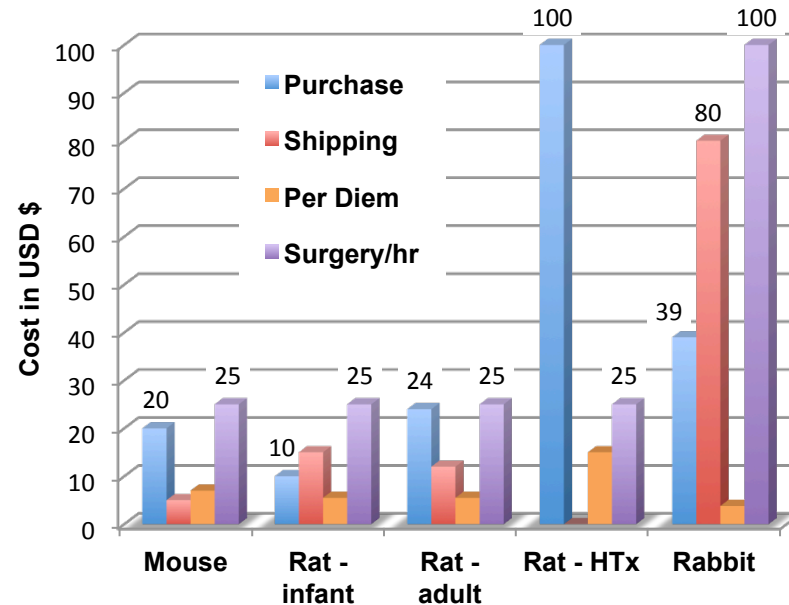
- **Logistics – study prevalence & cost**
- **Critical issues**
  - **Types of animal models & importance of a consistent hydrocephalus classification system**
    - **Obstructive/Intraventricular Hydrocephalus**
    - **Communicating/Extraventricular Hydrocephalus**
  - **Severity of ventriculomegaly**
  - **Variability of ventriculomegaly**
  - **Resolution & size of regions of interest**
  - **Application of clinical hardware**
  - **Need for correlative physiological & cellular data**
- **Summary & Recommendations**

## Citations by Species Since MRI Initiated 1990-2013



# Cost per Species

- University of Utah rates May 2013
- Note scale differences for small vs large animals
- Not include lab labor & institutional fees
- Shipping & Per Diem – consideration for multiple animals/cage
- Rat – HTx includes colony maintenance
- Mouse – no include congenital models





# How Animal Models Fit the New Classification of Hydrocephalus

Site of Obstruction	Severity	Animal Models
None (or <i>unknown</i> )	+ to +++	Knockout mice (McCarthy, TGF- $\beta$ 1, FGF-2), spontaneous mouse mutants (hyh), adult rats (CSF osmolarity)
For. of Monro	+ to ++	Tumor inoculation
Aqueduct of Sylvius	+ to +++	Neonatal rats (H-Tx, LEW/Jms, SD), mice (hyh, hy-3, SUMS/NP, FGF-2, TGF- $\beta$ 1); intraventricular blood
Outlets of 4 <sup>th</sup> ventricle	+ to +++	Intracisternal kaolin or blood in adult, developing and aged rat, hamster, guinea pig, rabbit, cat, dog, pig, sheep, monkey
Basal cisterns	+ to ++	Adult rats, dogs, sheep, neonatal/fetal mice (HB-EGF); subarachnoid blood
Arachnoid villi	+ to ++	Adult & developing rat
Venous outflow	+ to ++	Adult rabbit, dog

# Pulsatile Cerebrospinal Fluid Dynamics in the Human Brain

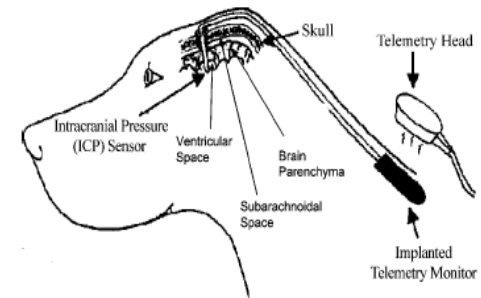
Andreas A. Linninger, Cristian Tsakiris, David C. Zhu, Michalis Xenos, Peter Roycewicz, Zachary Danziger, and Richard Penn

IEEE Transactions on Biomedical Engineering 52 (4): 557, 2005

Abstract (excerpts): Considerable controversy exists about fluid and pressure dynamics, and about how the brain responds to changes in flow patterns and compression in hydrocephalus. This paper presents a new model based on the first principles of fluid mechanics. This model of fluid-structure interactions predicts flows and pressures throughout the brain's ventricular pathways consistent with both animal intracranial pressure (ICP) measurements and human CINE phase-contrast magnetic resonance imaging data. The computations provide approximations of the tissue deformations of the brain parenchyma. The model also quantifies the pulsatile CSF motion including flow reversal in the aqueduct as well as the changes in ICPs due to brain tissue compression. It does not require the existence of large transmural pressure differences as the force for ventricular expansion. Finally, **the new model gives an explanation of communicating hydrocephalus** and the phenomenon of asymmetric hydrocephalus.

Kaolin injected into the cisterna magna of 6 adult dogs; 2 died prematurely; 4 developed “chronic” hydrocephalus (20 days).

*“The autopsy of the animal showed **expanded ventricles consistent with acute communicating hydrocephalus**. The SAS was found to be clogged with kaolin. In effect, kaolin injection blocked the CSF reabsorption through the SAS.”*



**JPM: not “communicating” hydrocephalus b/c intracisternal kaolin blocks the 4<sup>th</sup> ventricle outlets as well; difference could have profound effects on CSF physiology.**

## **Congenital hydrocephalus revealed in the inbred rat, LEW/Jms**

Sasaki,S.; Goto,H.; Nagano,H.; Furuya,K.; Omata,Y.; Kanazawa,K.; Suzuki,K.; Sudo,K.; Collmann,H.  
Neurosurgery 13 (5): 548-554, 1983

Abstract: We studied the development of congenital hydrocephalus found in a colony of an inbred strain of Wistar-Lewis rats (LEW/Jms) at various intervals after birth. The disorder was transmitted as a simple recessive mendelian character. Hydrocephalic neonates were recognized 2 days after birth by stretching of the skin over the head. Death usually occurred between 10 and 20 days of age. The findings suggested the possibility of a disturbance of cerebrospinal fluid circulation resulting from **primary occlusion of the 3rd or lateral ventricles during embryological development. In later phases, the hydrocephalus was aggravated by obliteration of the subarachnoid space and by stenosis of the aqueduct occurring secondary to compression of these structures from increased pressure within the brain. In some animals, external hydrocephalus occurred as a result of rupture of the occipital pole and the establishment of a direct communication between the lateral ventricles and the subdural space.**

- **Possible evolution of lateral/3<sup>rd</sup> ventricle obstruction (foramen of Monroe?) to aqueductal stenosis to SAS communicating hydrocephalus.**
- **Strong male bias (Jones HC et al, CSF Research, 2005)**

## Occlusion of the sagittal sinus in craniectomized rabbits

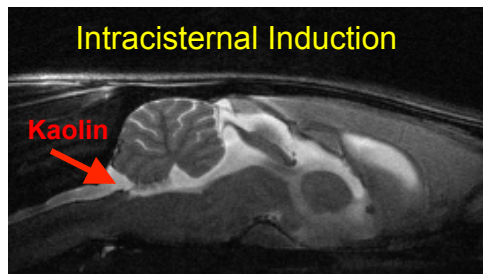
Olivero WC, Asner N.

Child's Nervous System 8: 307-309, 1992

Abstract: Most attempts at production of hydrocephalus in experimental animals by obstructing venous sinuses have failed. In adult humans, venous sinus occlusion usually results in the clinical syndrome of pseudotumor cerebri with small or normal sized ventricles. However, in children less than 18 months old with venous sinus hypertension, ventriculomegaly has been reported. We examined the change in ventricular size in craniectomized animals (simulating children with open sutures) with occlusion of the superior sagittal sinus. New Zealand rabbits weighing 1500-1800 g were anesthetized ... and a craniectomy performed ... The dura was exposed overlying both cerebral hemispheres and the superior sagittal sinus from its origin to the torcular ... and then the sinus was coagulated with bipolar cautery and transected; the scalp was then closed. All animals were allowed 5-7 days to recover, then ultrasound was used to assess ventricular size. We observed a small but statistically significant increase in ventricular size in the experimental group compared to the control group. **This model provides evidence that venous sinus occlusion in animals with expandable crania can produce ventriculomegaly.**

# Neonatal vs. Juvenile Rat Models

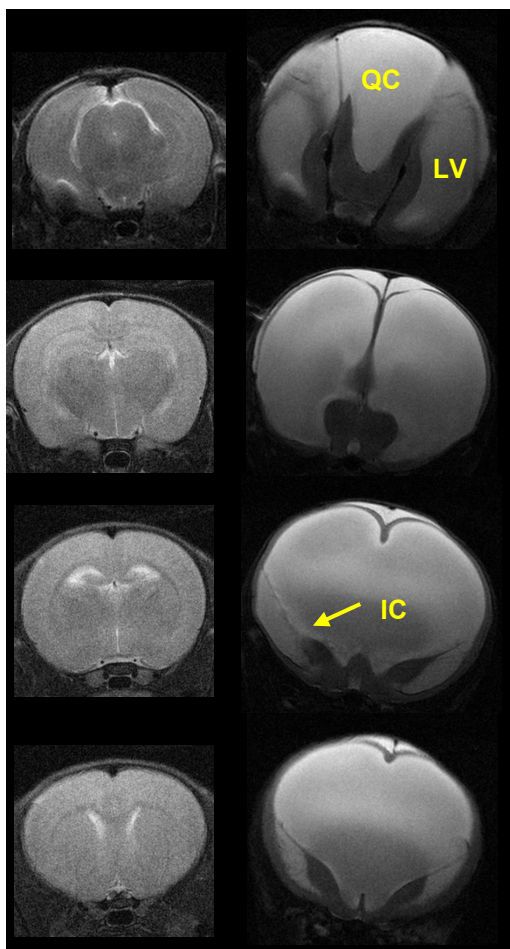
Kaolin @ 3 wks



Kaolin @ 1 day

Age-matched Control

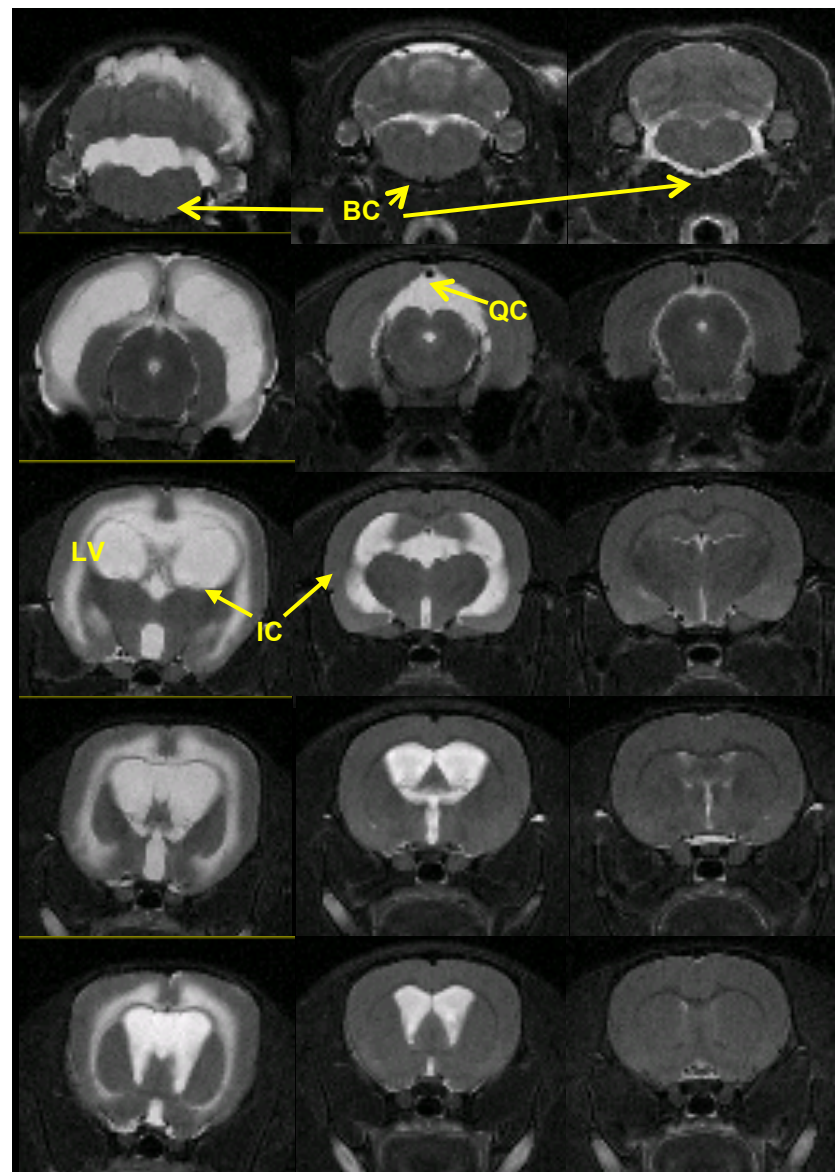
"Supreme" Hydrocephalus



Severe Hydrocephalus

Moderate Hydrocephalus

Age-matched Control



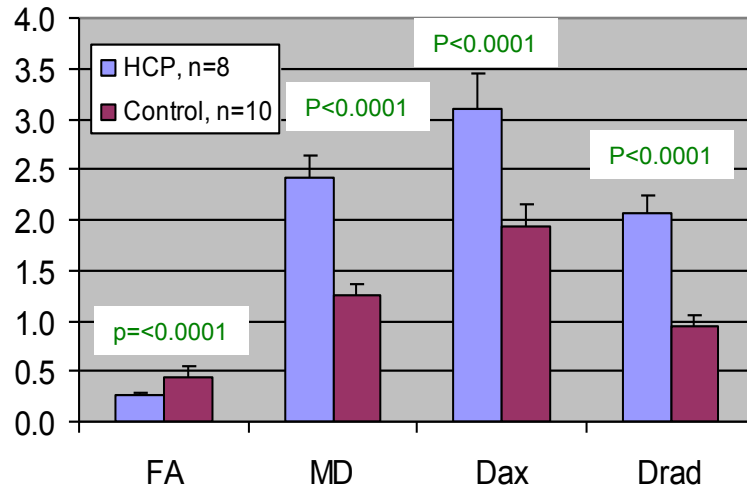
## Key Differences

- Expandable skull in neonate
- Severity – may not be clinically relevant
- WM thinning – DTI difficult/impossible
- WM edema
- Induction more difficult in neonate
- \* *Modeling different developmental stages*

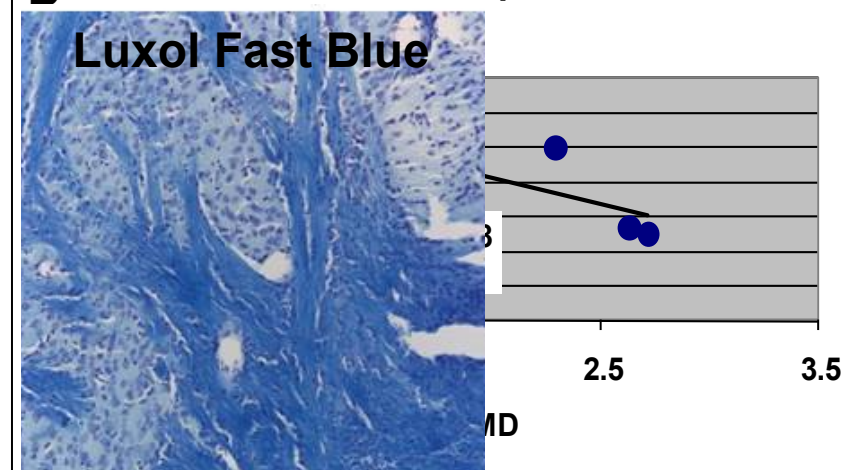
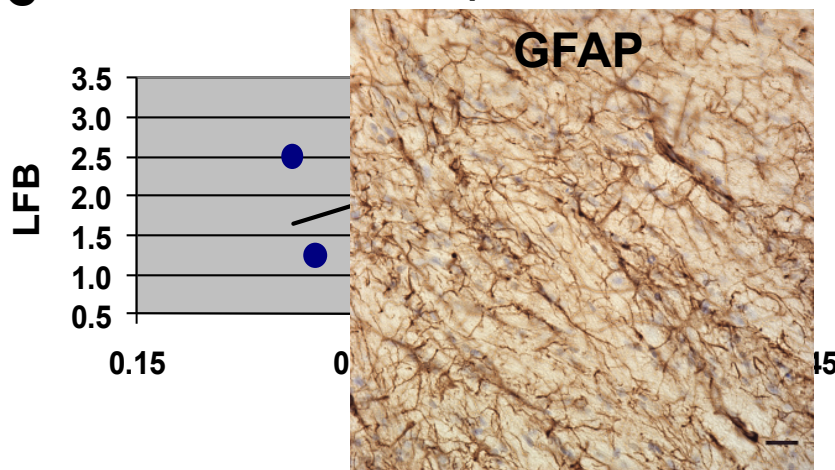
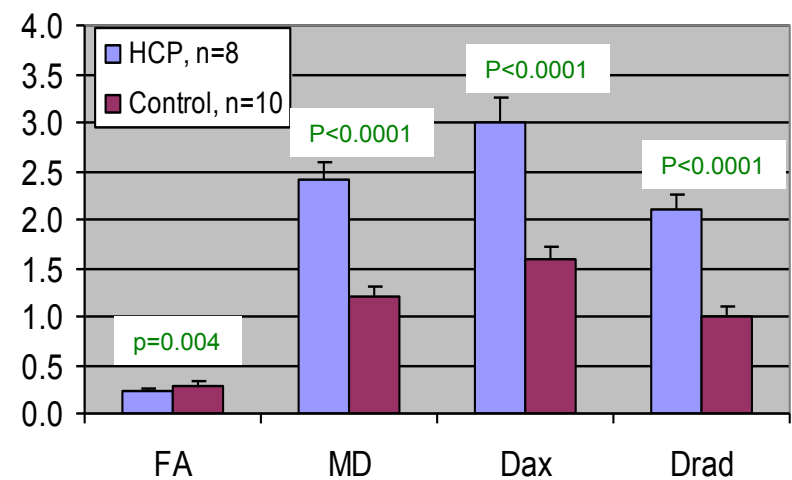


# DTI:Cytopathology Correlations in Neonatal Rats

## Corpus Callosum (P7-9)



## Internal Capsule (P7-9)



# Severity of Ventriculomegaly

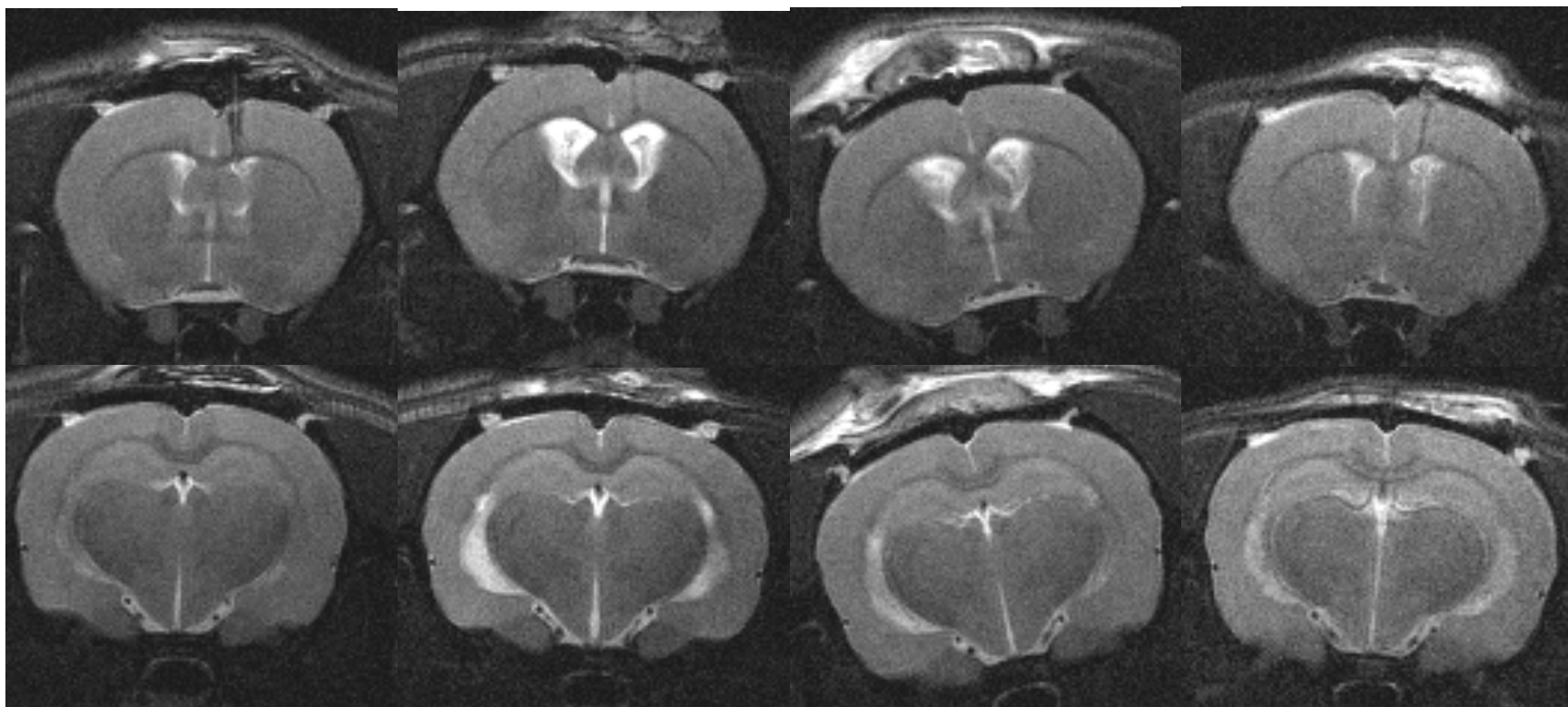
MRI after 12 days of ventricular infusions

aCSF

FGF-2

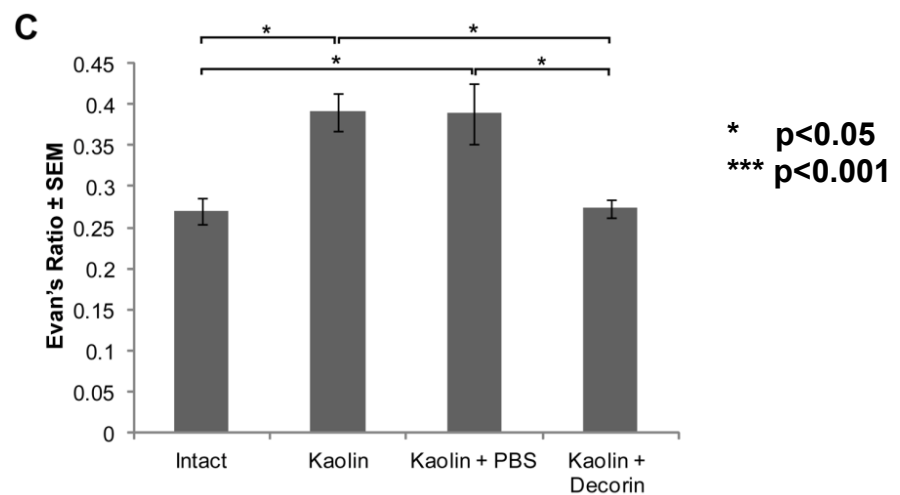
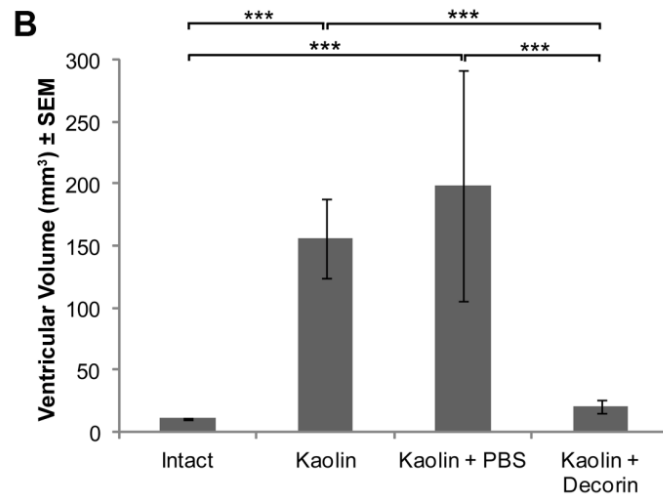
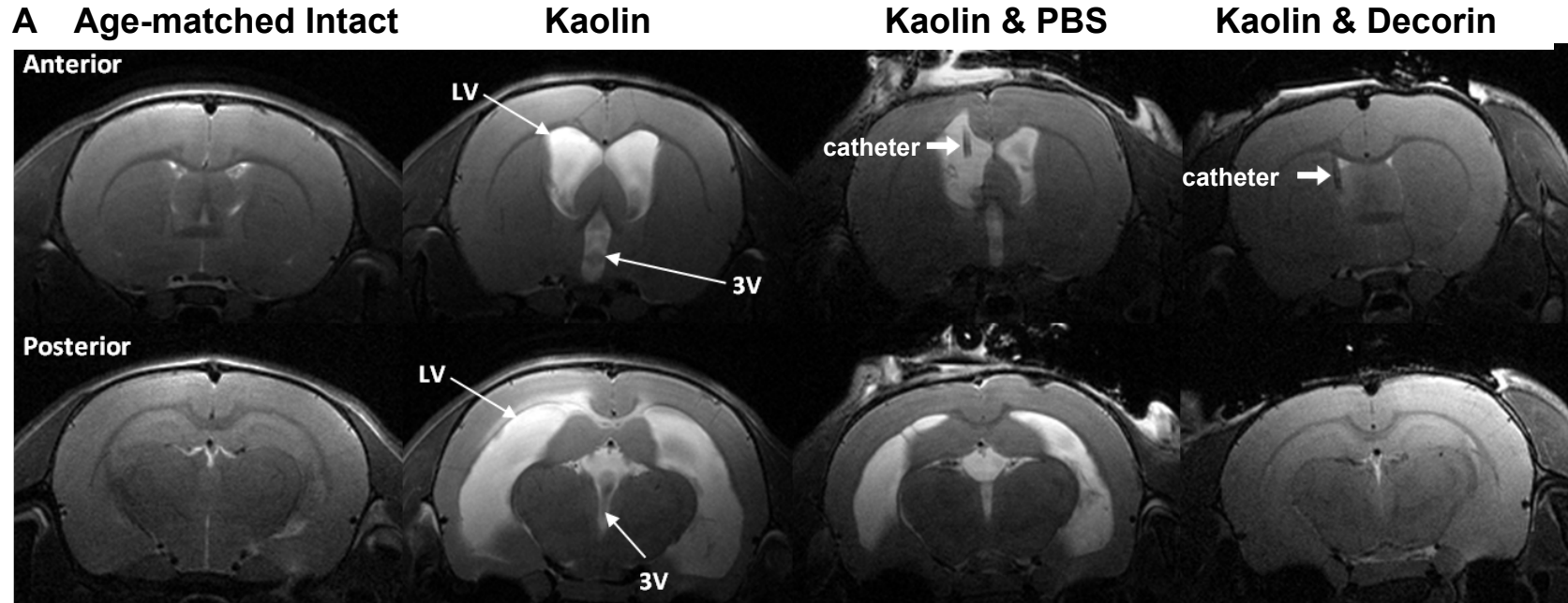
10kd Dextran

40kd Dextran



Satish Krishnamurthy , Jie Li , Lonni Schultz and James P McAllister II. Intraventricular infusion of hyperosmolar dextran induces hydrocephalus: a novel animal model of hydrocephalus. *Cerebrospinal Fluid Research* 6: 16, 2009.

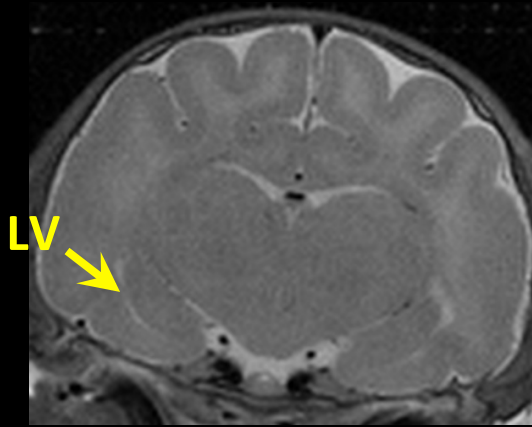
# Decorin Prevents Ventriculomegaly



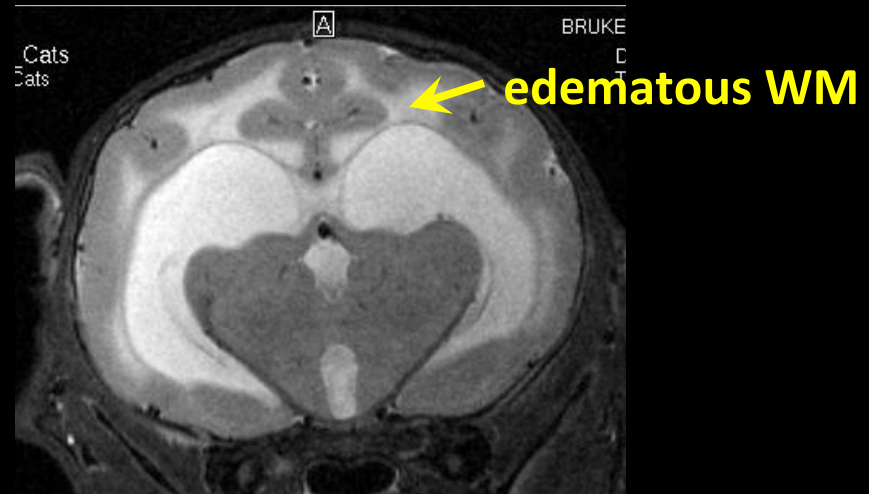


# Neonatal Kitten Intracisternal Model

**Saline Control**



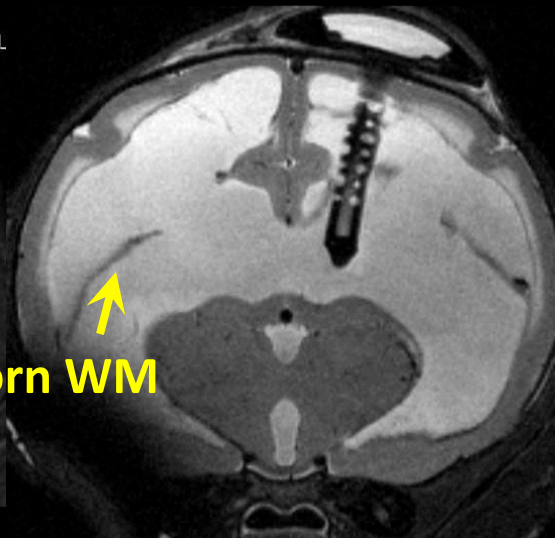
**Pre-Op 7d post-kaolin**



**Post-Op 7 days**



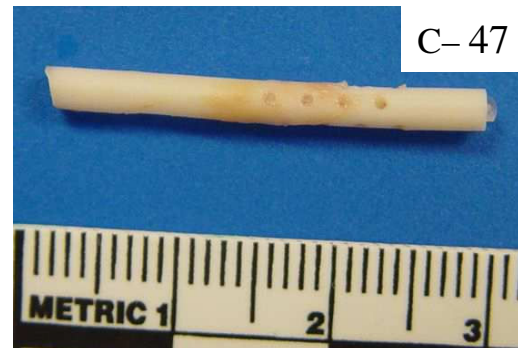
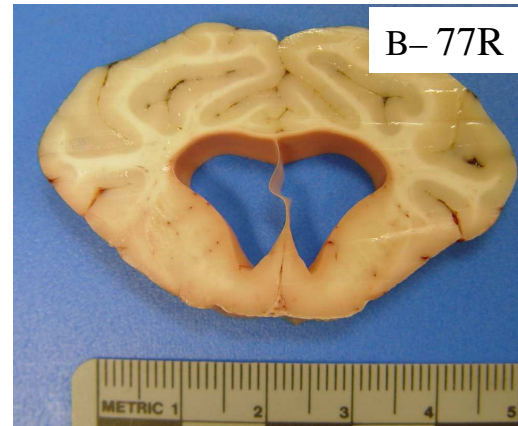
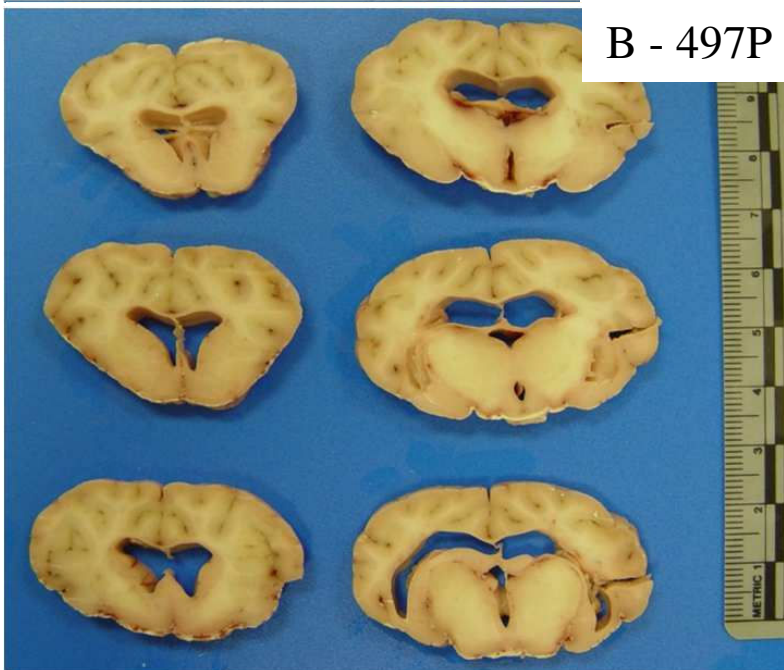
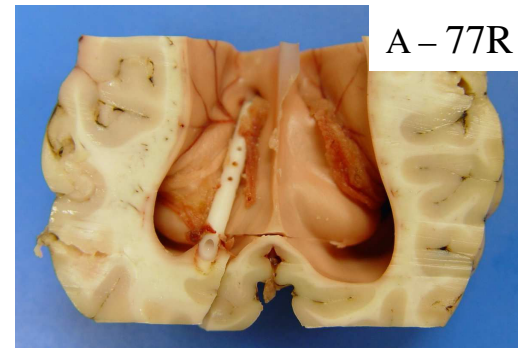
**Post-Op 42 days**



**Post-Op 63 days**



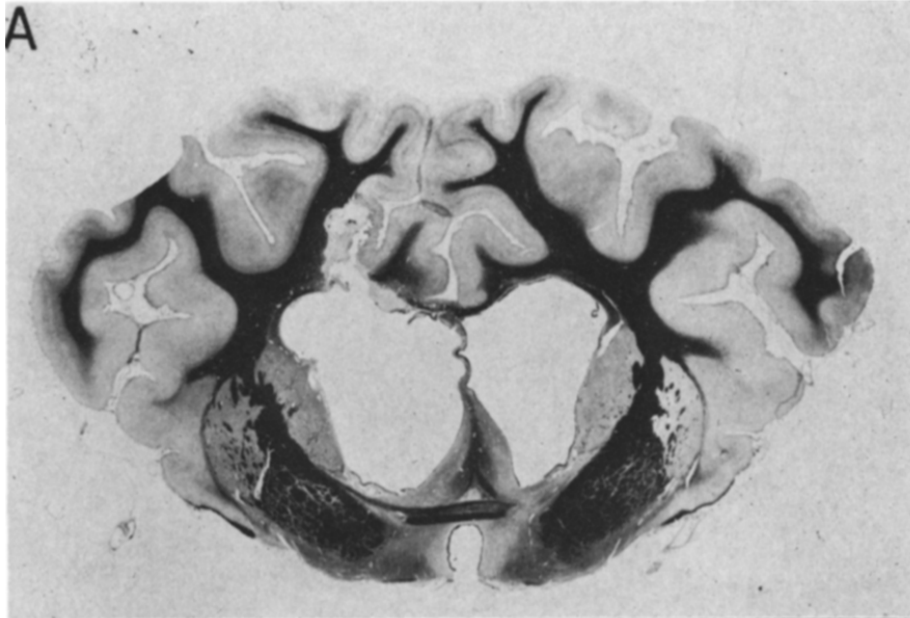
# Adult Sheep Model – courtesy Miles Johnston et al



# Adult Sheep Intraventricular Pressure Model

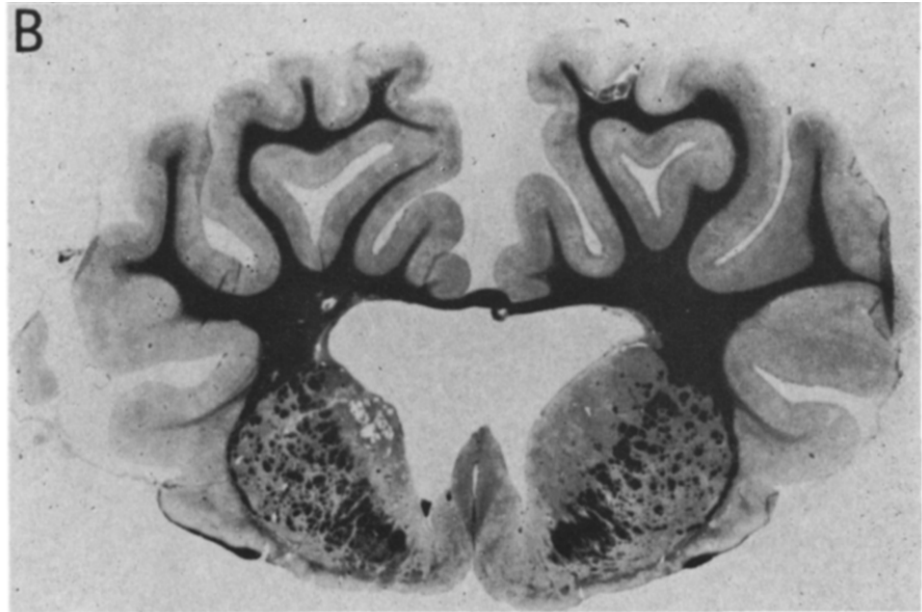
## Animal 15

20 h balloon pumping  
mlCP = 4 cm H<sub>2</sub>O; plCP = 3.5 cm H<sub>2</sub>O  
7 d post-balloon



## Animal 17

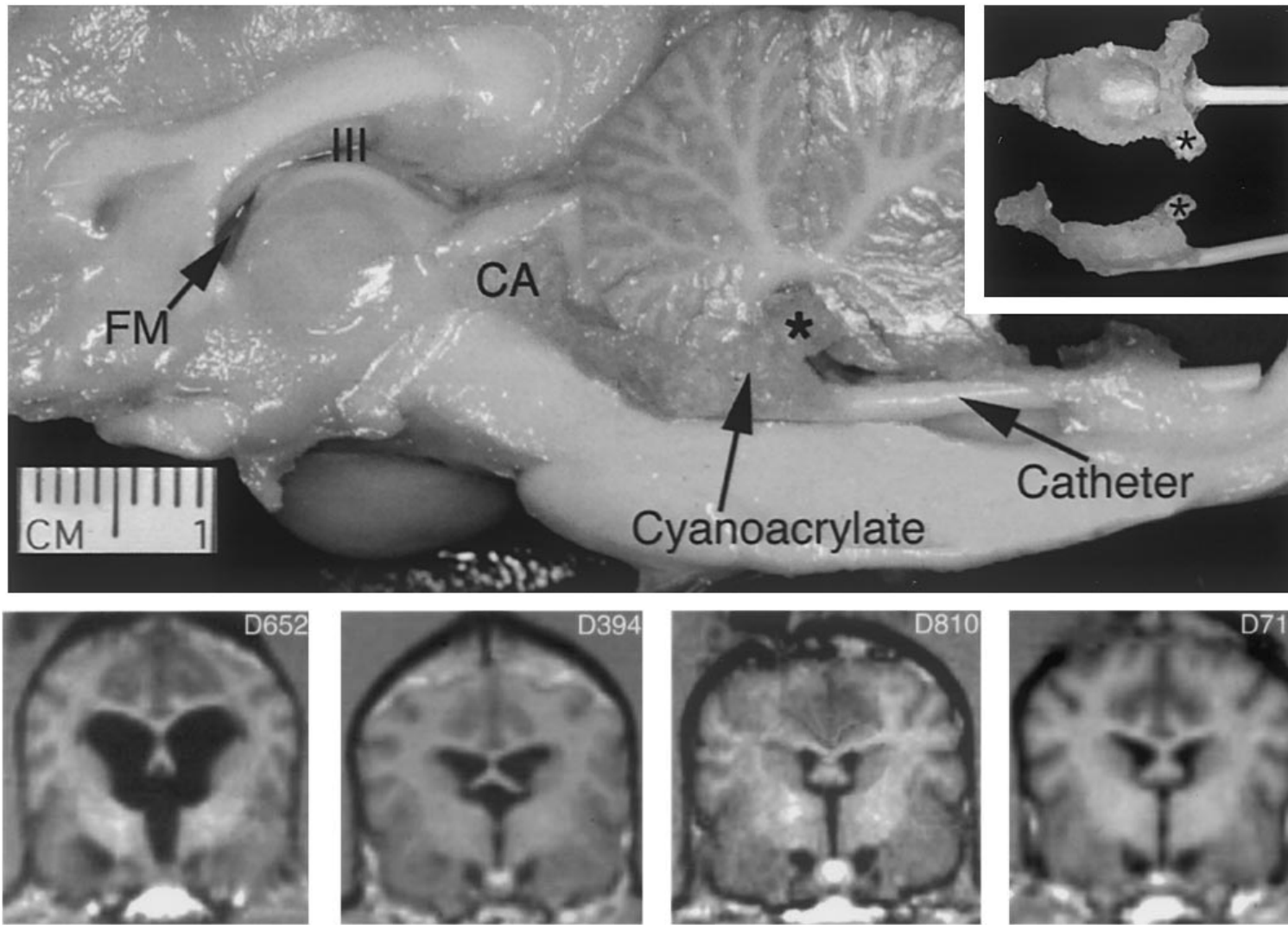
20 h balloon pumping  
mlCP = 3.5 cm H<sub>2</sub>O; plCP = 2.0 cm H<sub>2</sub>O  
4 d post-balloon



DiRocco C, Pettorossi VE, Caldarelli M, Mancinelli R, Velardi F. Communicating hydrocephalus induced by mechanically increased amplitude of the intraventricular CSF pressure: experimental studies. *Exp Neurol* 59: 40-52, 1978.

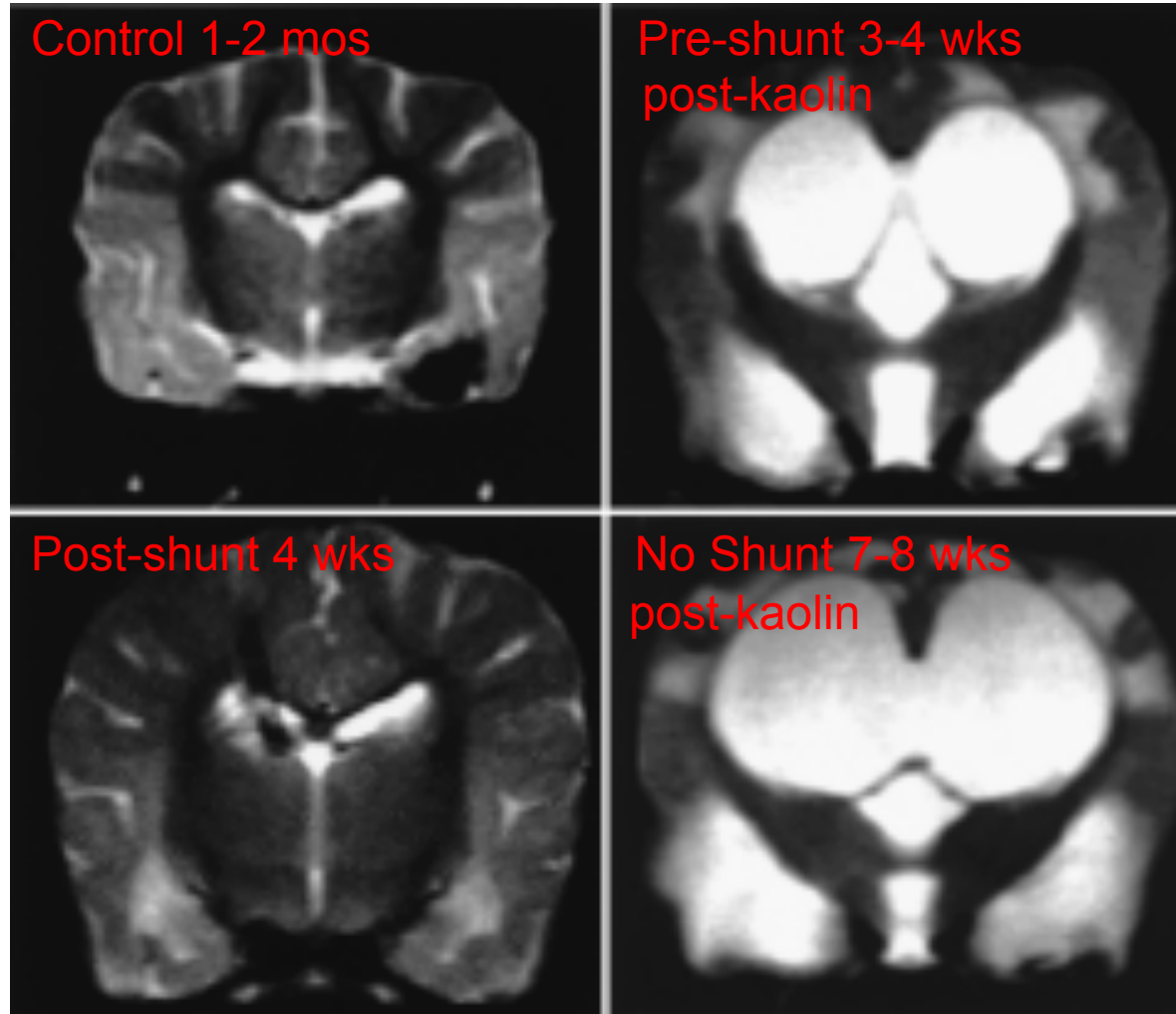


# Canine Hydrocephalus Model



Johnson MJ, Ayzman I, Wood AS, Tkach JA, Klaushie J, Skarupa DJ, McAllister JP, Luciano MG. Development and characterization of an adult model of obstructive hydrocephalus. *J Neurosci Methods* 91: 55-65, 1999

# Young Canine Hydrocephalus Model



Aoyama Y, Kinoshita Y, Yokota A, Hamada T, Neuronal damage in hydrocephalus and its restoration by shunt insertion in experimental hydrocephalus: a study involving the neurofilament-immunostaining method. *J Neurosurg Pediatr* 104: 332-339, 2006.

# Summary & Recommendations

Issue	Problem(s)	Recommendations
Hydrocephalus Type	Clinically relevant ID of CSF obstruction site; different physiol. effects	All models; MRI confirmation of obstruction site; follow the literature
Ventriculomegaly	Some models too severe	Sacrifice or shunt early
Variability	Progression variable; age-dependent	MRI quantification (ventricular volume preferred); follow literature
Cost	Incomplete studies (n<5); no studies; human relevance (rodent focus)	Form collaborative groups; include clinicians; lobby NIH; participate in NIH study sections
Brain Size	Resolution of key structures (i.e. perivent. WM)	Choose appropriate model; extend scan time; ex vivo scan (DTI)
Congenital Models	Too small; short survival	Improve MRI resolution; shunt treatments
Treatment Studies	Clinical hardware requires large models	Utilize sheep or rabbits; consider animal rights objections to cats/dogs



# Thank You!

