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Division of Pediatric Neurosurgery

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Utility of MRI in Assessing Animal Models of Hydrocephalus

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Disclosures

- No conflicts of interest
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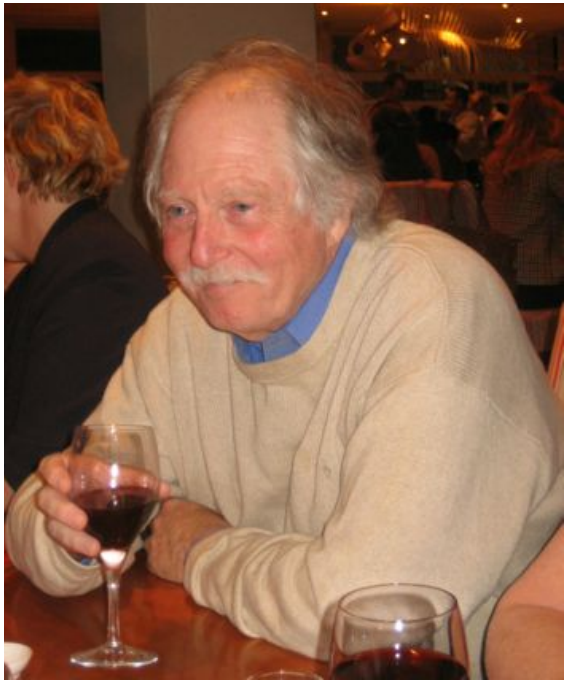
- Member: Hydrocephalus Association Medical Advisory Board; Aqueduct Neurosciences, Inc. Board
- Co-founder, OmniShunts LLC
- President-Elect, Society for Research into Hydrocephalus and Spina Bifida



Recent MRI Applications in Animal Models of Hydrocephalus

- **Anatomical quantification of ventriculomegaly – critical for documentation of:**
  - **inherent variability and severity** – especially in adult vs pediatric (fixed vs expandable skull)
  - **regional differences** - ventricular volume better than Evan's ratio
  - **temporal progression** – slow usually becomes chronic
  - **treatment outcome** – shunting & pharmacological intervention
- **Fluid flow and pulsatility** – CSF & blood (capillary)
- **White matter integrity** – DTI (cellular basis unknown)
- **Non-invasive ICP** – large animals
- **Biomechanics and compliance** – MR elastography

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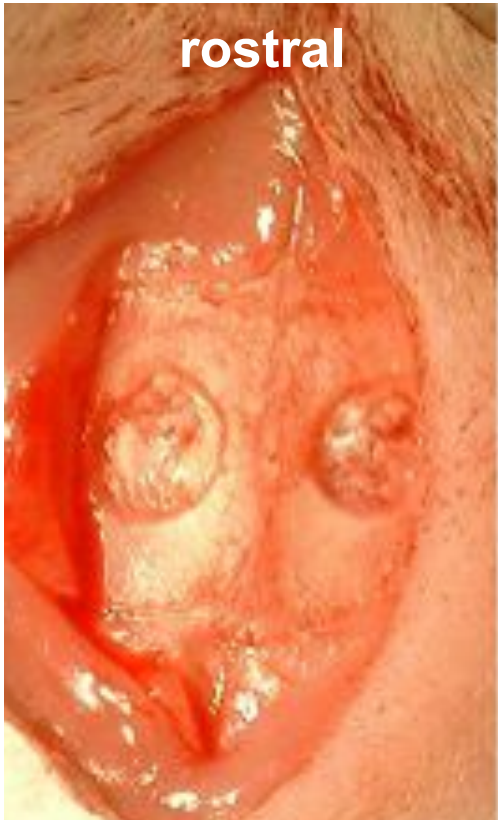
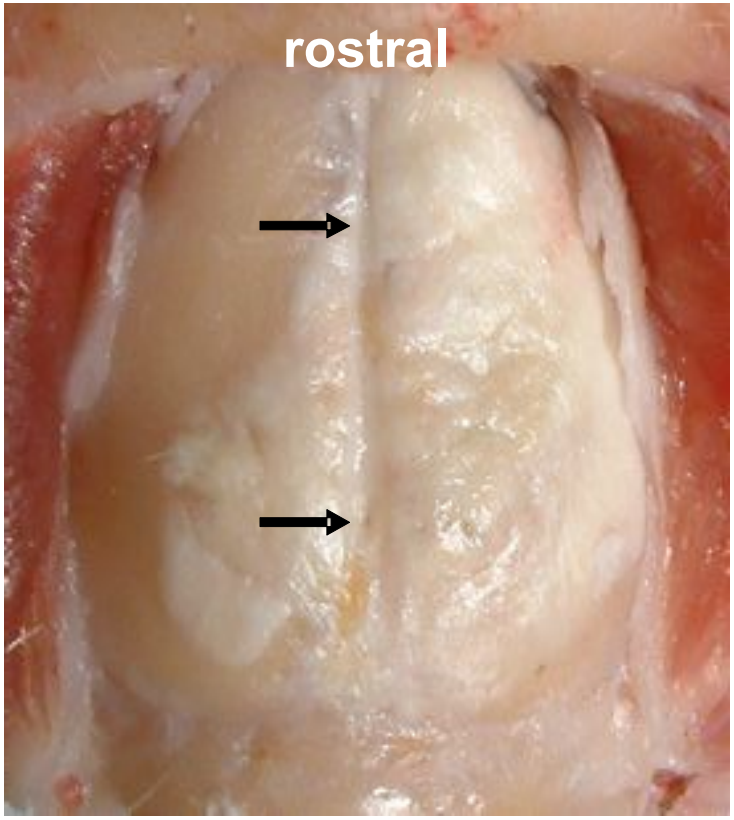
Current NEEDS for MRI in Animal Models of Hydrocephalus

1. **Physiological monitoring** – oximetry, temperature, HR, respiration, i.e. differential effects of anesthetics
2. **Chronic studies**, i.e. >100 days post-induction/treatment – protracted ventriculomegaly, pediatric-adult progression
3. **Resolution < 0.1mm**
   - ✧ detection of CSF obstruction sites – importance of the Rekate classification
   - ✧ catheter placement
   - ✧ DTI of thinned periventricular white matter
   - ✧ mouse models
   - ✧ Cellular alterations, i.e. heterotopias, stem cell implants, fibrosis/ inflammation
   - ✧ shunt obstruction
4. **ICP measurements** – important but very difficult in small animals
5. **Biomechanical assessments** – compliance, ICP, DENSE technique?
6. **Functional MRI** – vs behavioral measurements

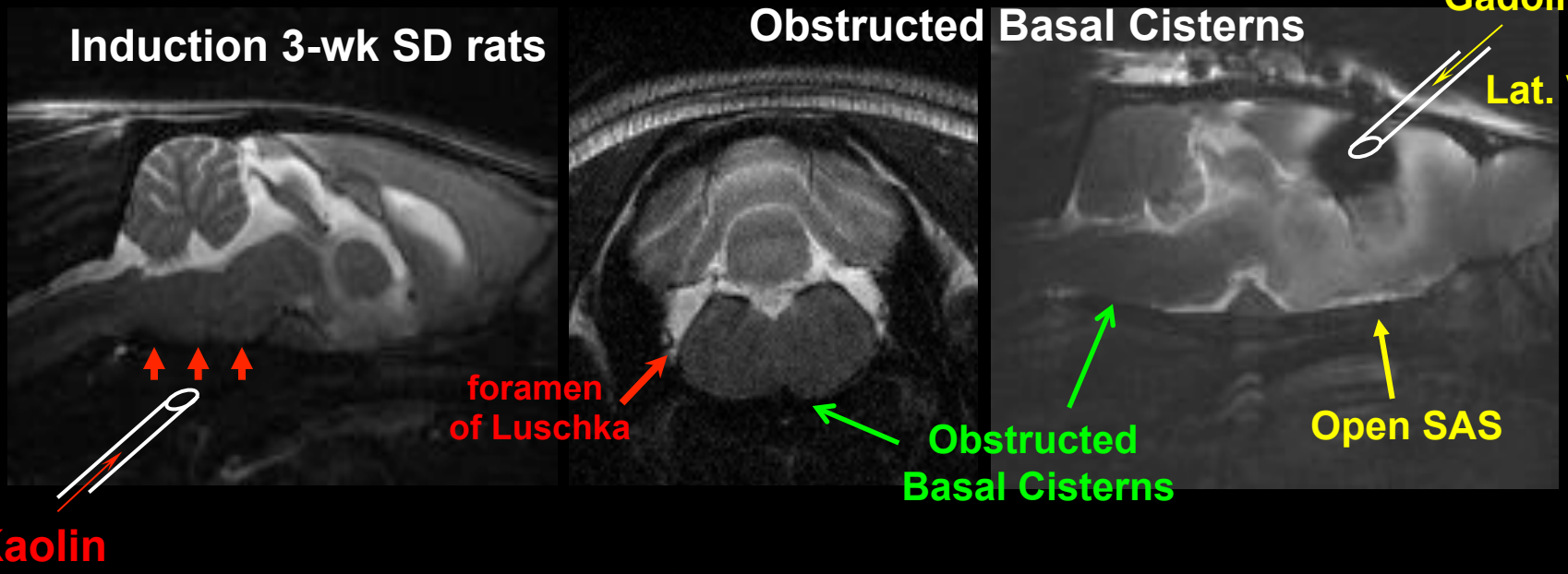
Dorsal Hemisphere “Convexity” Obstruction





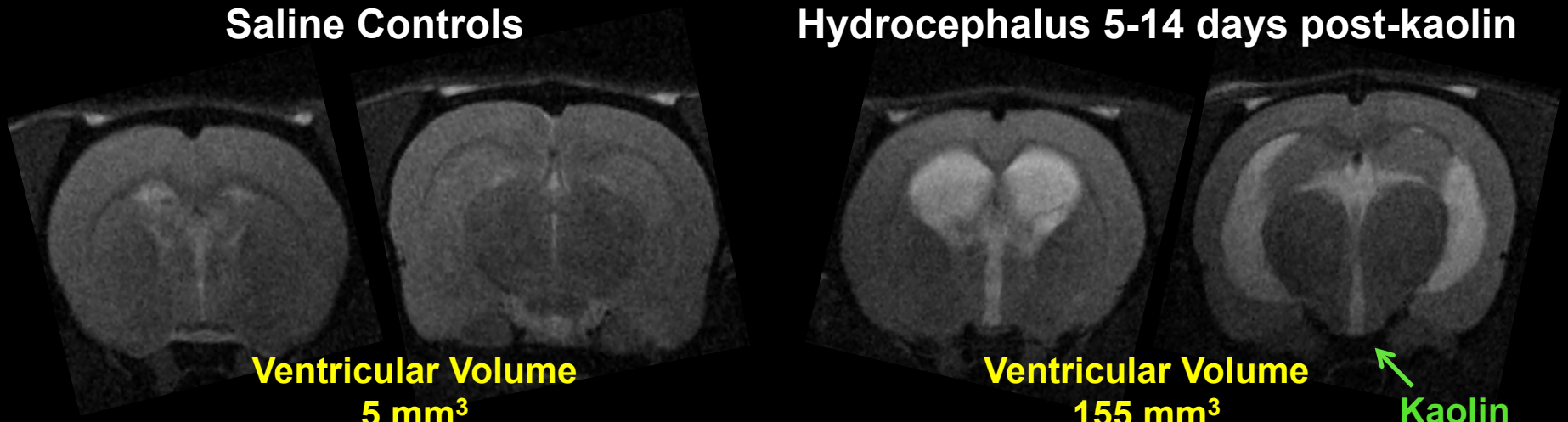
- Sprague-Dawley Female Rats, 225–250 g (3 mos.)
- 3.0 mm dia. bilat. craniotomies over cerebral hemisphere; A blunt tip 4-0 nylon suture inserted to separate partitions in the subarachnoid space (SAS)
- A blunt tip, curved needle (30G) inserted into SAS, 50–60 μl of 25% kaolin solution injected at about 10 μl per second
- Bone flaps replaced, secured in place with Surgicel™, Survival period = 1-385 days

Kaolin Obstructs Basal Cisterns



Saline Controls

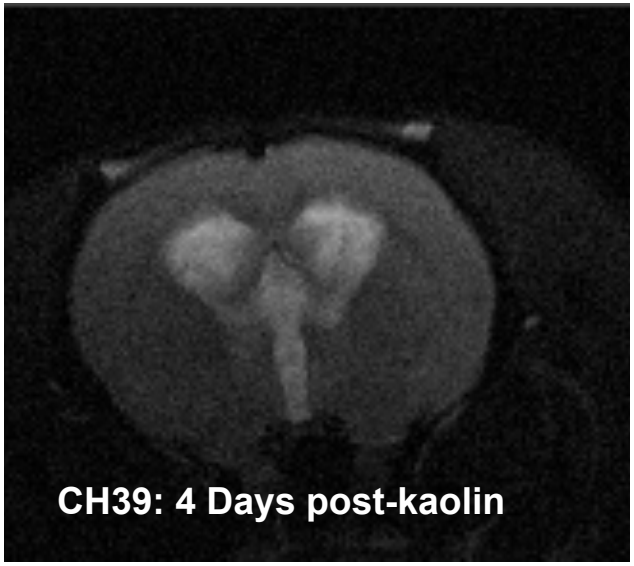
Hydrocephalus 5-14 days post-kaolin

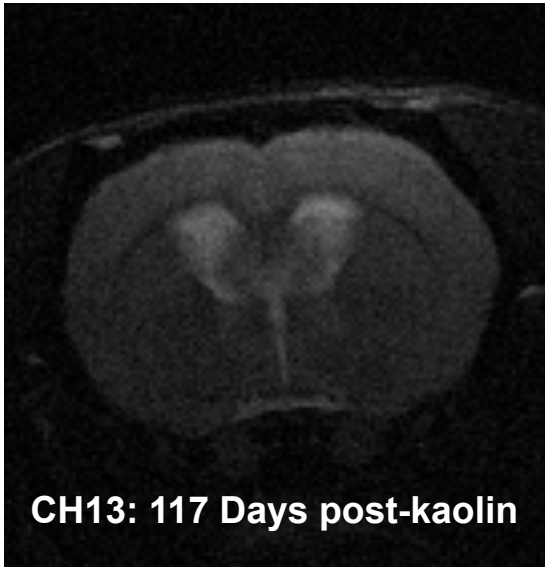


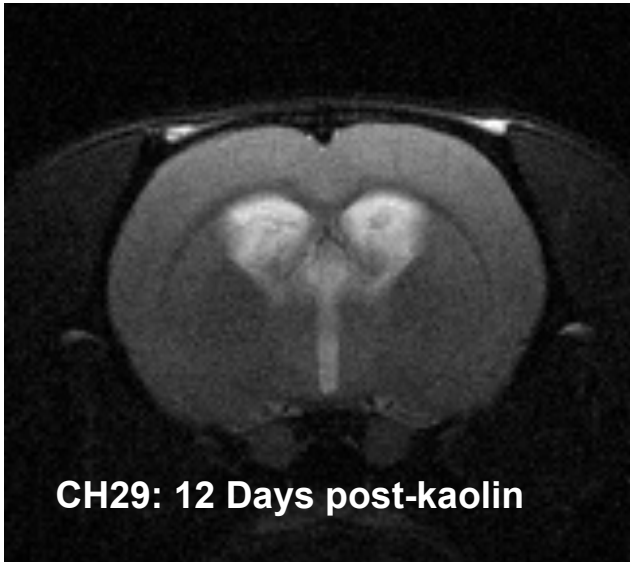
Progression of Ventriculomegaly

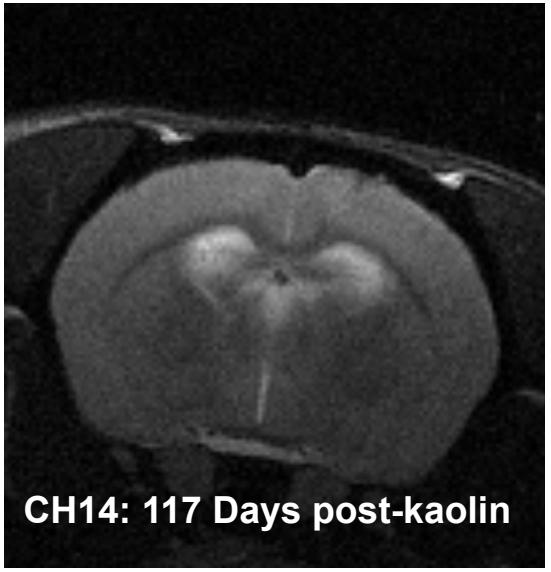
Rapid – Basal Cistern

Slow – Cortical









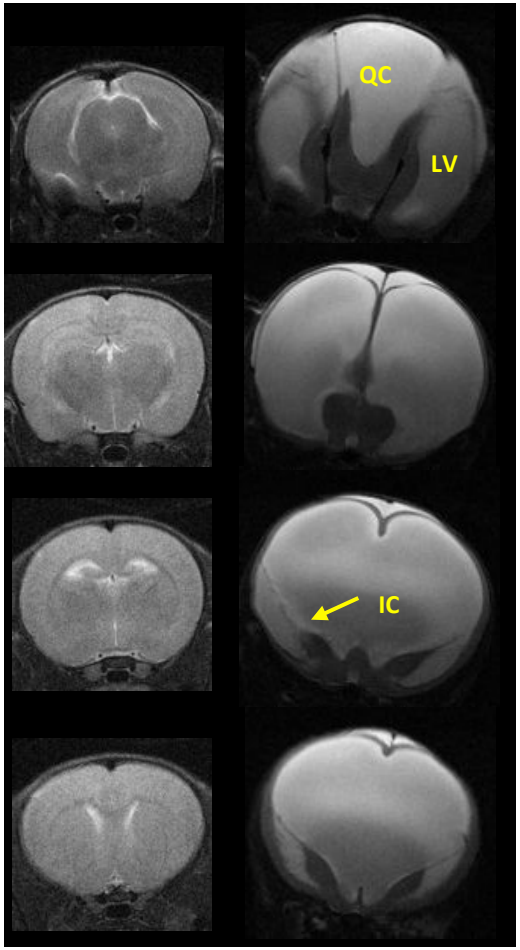
Neonatal vs. Juvenile Rat Models

Key Differences

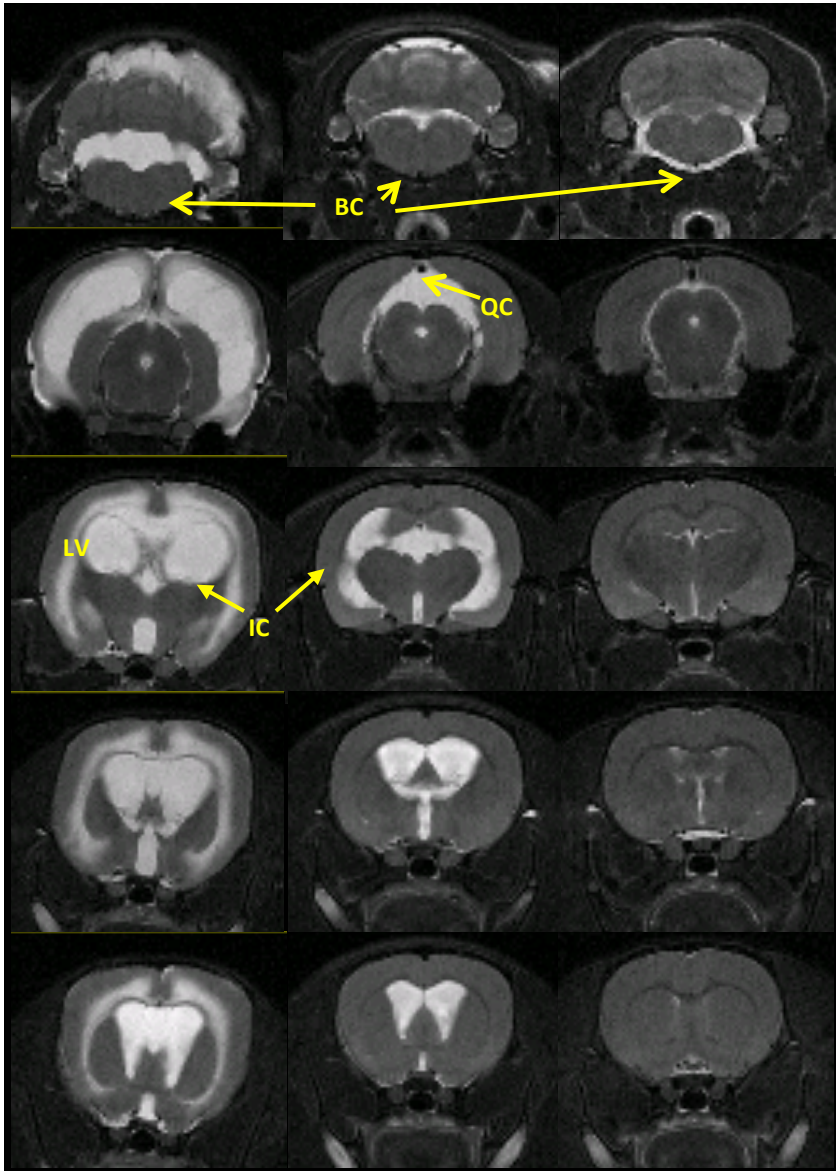
- Expandable skull in neonate
- Severity – may not be clinically relevant
- WM thinning – DTI difficult/impossible
- WM edema
- Induction more difficult in neonate

* *Modeling different developmental stages*

Kaolin @ 1 day



Kaolin @ 3 wks



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Relative Severity of Ventriculomegaly & MRI Resolution

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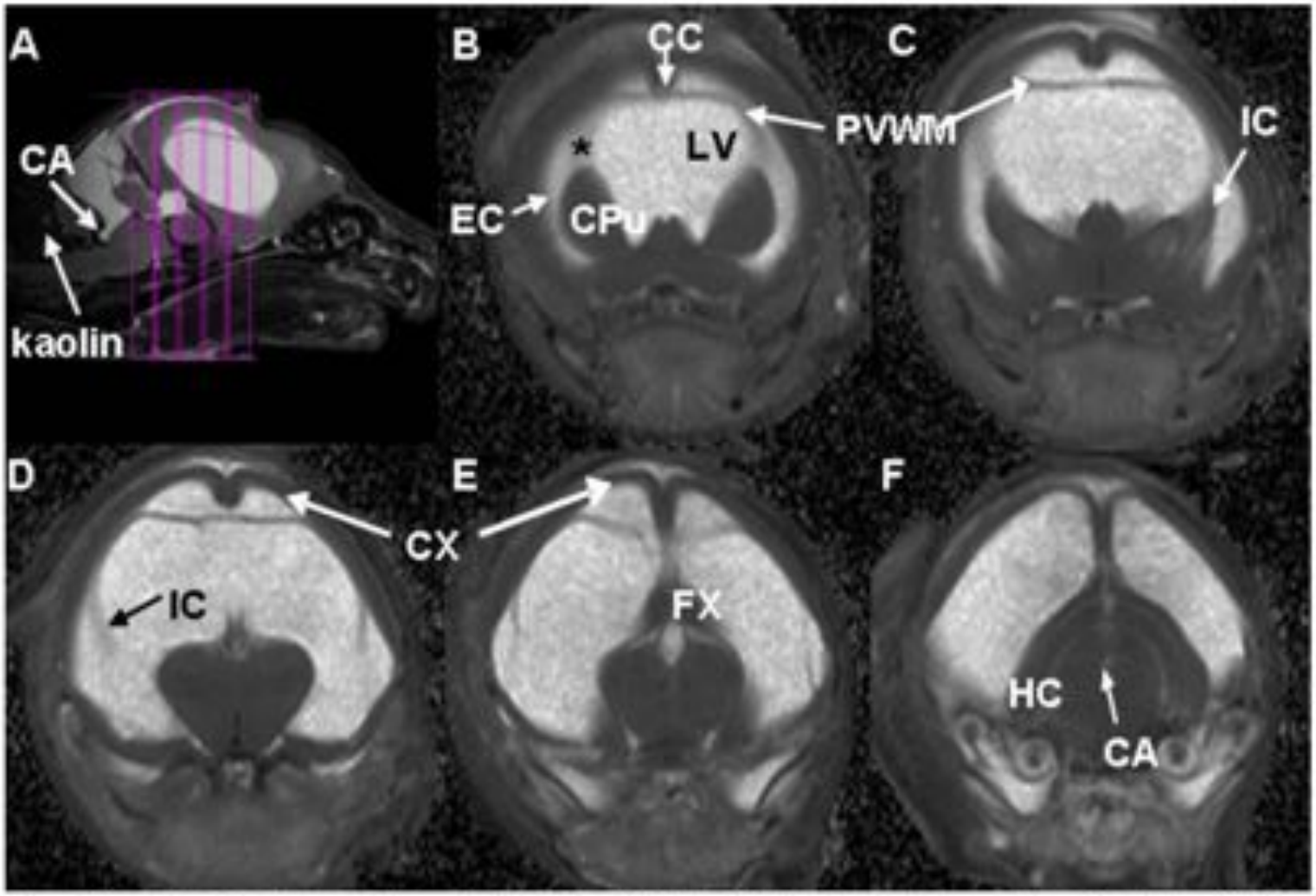

Figure 2 Mean diffusivity maps of hydrocephalic rats at postnatal day 11. The mid-sagittal image (A) shows the location of the five coronal slices (B-F) arranged from rostral to caudal. The expansion of the lateral ventricle and the posterior recess of the cerebral aqueduct (CA) can also be seen. Abbreviations: CC, corpus callosum; CPu, caudate-putamen; CX, cortex; EC, external capsule; FX, fornix; IC, internal capsule; HC, hippocampus; LV, lateral ventricle; PVWM, periventricular white matter.

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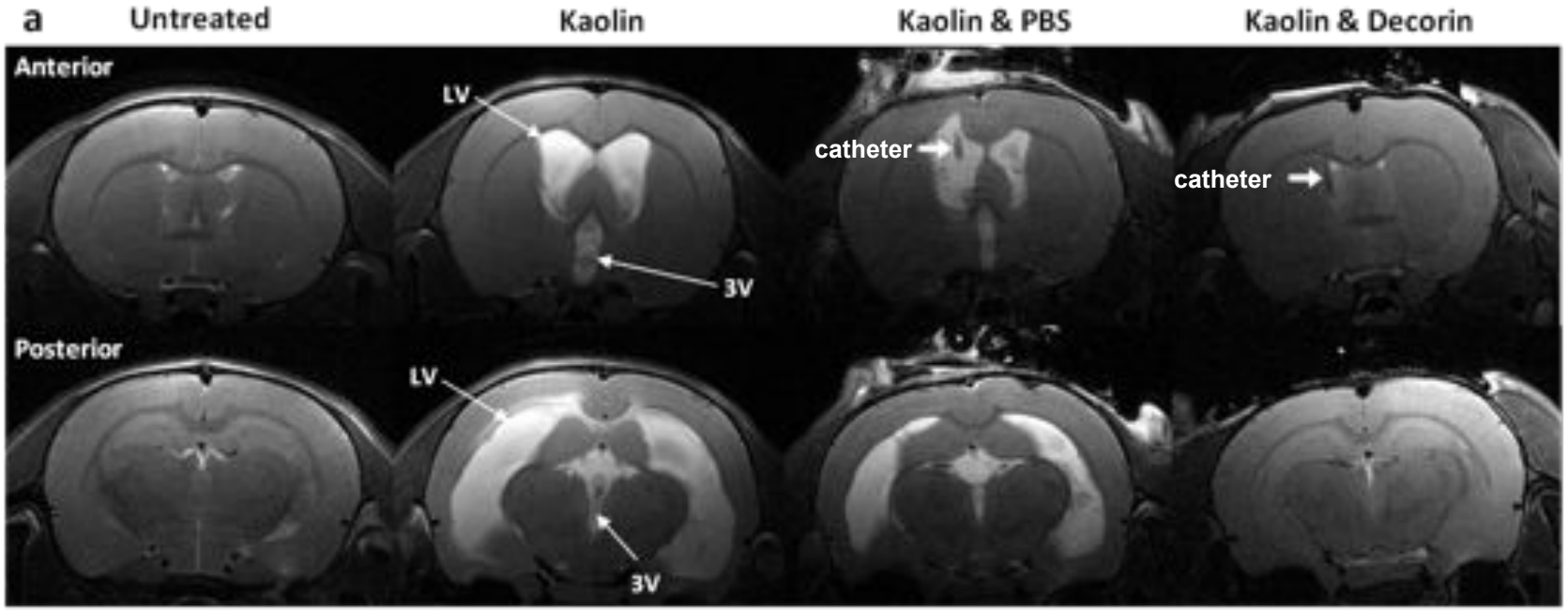
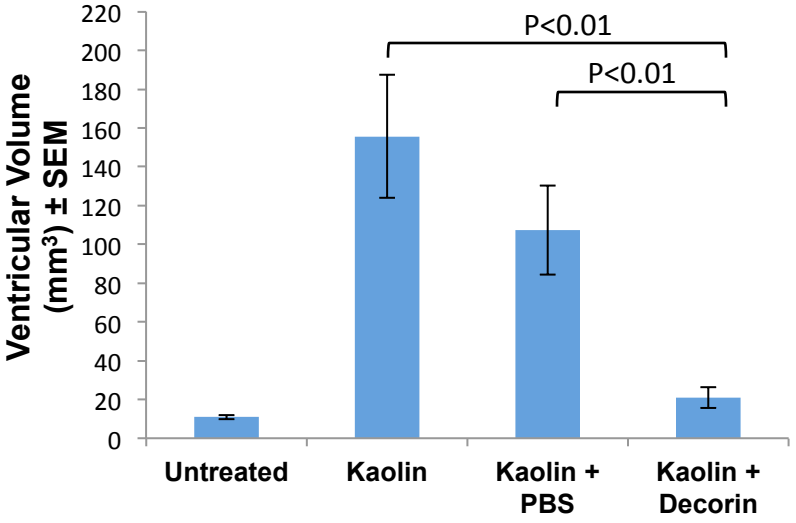
Decorin Effects in *Pediatric* Extraventricular Hydrocephalus

UNIVERSITY OF BIRMINGHAM

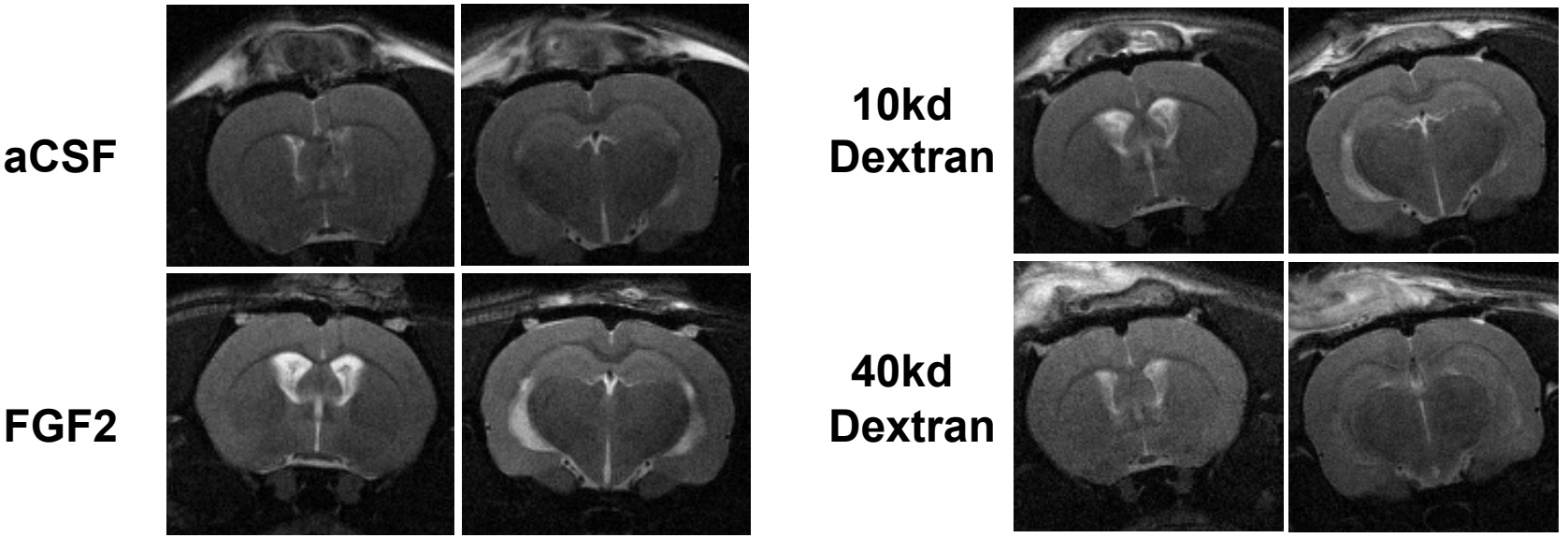




Hannah Botfield, Ana Maria Gonzalez, Osama Abdullah, Anders Dæhli Skjolding, Martin Berry, James Pat McAllister II and Ann Logan. Decorin prevents the development of juvenile communicating hydrocephalus. *Brain* 136; 2842–2858, 2013

Severity of Hydrocephalus

Is this "Hydrocephalus"?



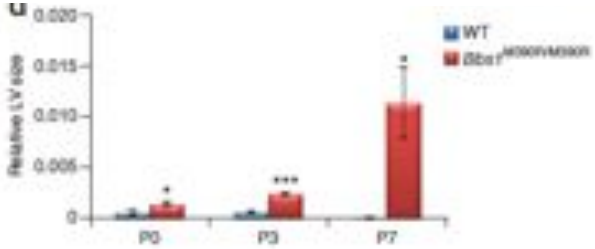
Satish Krishnamurthy, Jie Li, Lonni Schultz, James P McAllister II. Intraventricular infusion of hyperosmolar dextran induces hydrocephalus: a novel animal model of hydrocephalus. *Cerebrospinal Fluid Research* 2009, 6:16

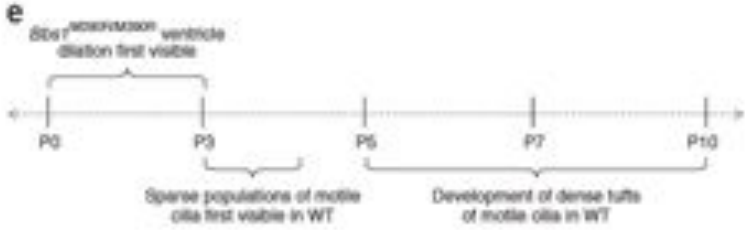
Relative Severity of Ventriculomegaly

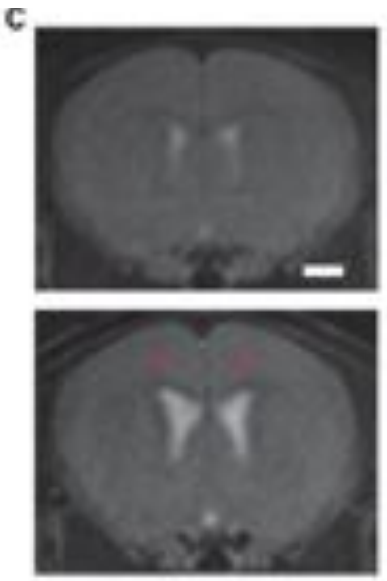
nature medicine

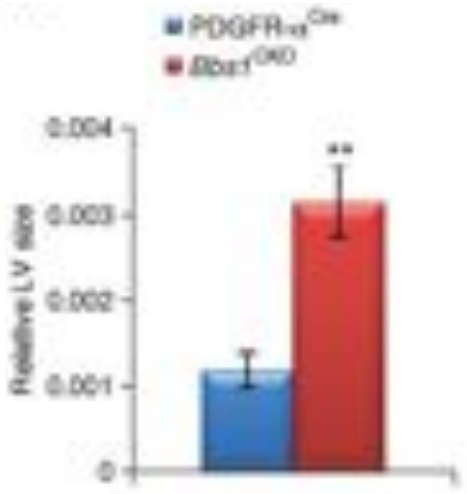
Abnormal development of NG2^{+}PDGFR-α^{+} neural progenitor cells leads to neonatal hydrocephalus in a ciliopathy mouse model

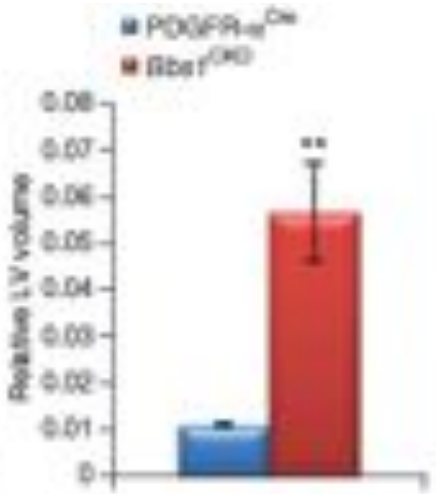
Calvin S Carter[1,10], Timothy W Vogel[2,10], Qihong Zhang[3,4], Seongjin Seo[4,5], Ruth E Swiderski[3,4], Thomas O Moninger[6], Martin D Cassell[7], Daniel R Thedens[8], Kim M Keppler-Noreuil[3], Peggy Nopoulos[9], Darryl Y Nishimura[3], Charles C Searby[3,4], Kevin Bugge[3,4] & Val C Sheffield[3,4]











Relative Severity of Ventriculomegaly

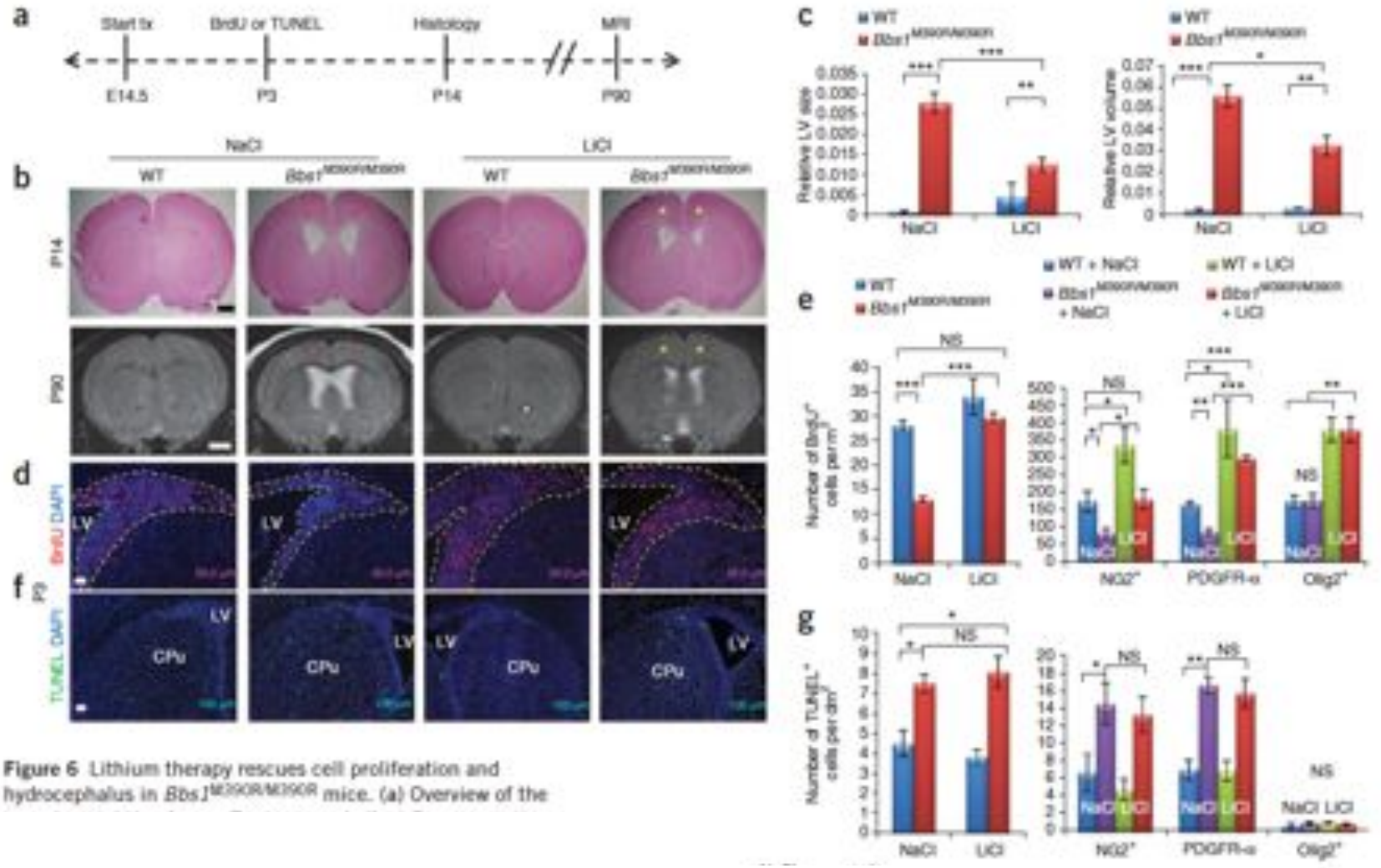
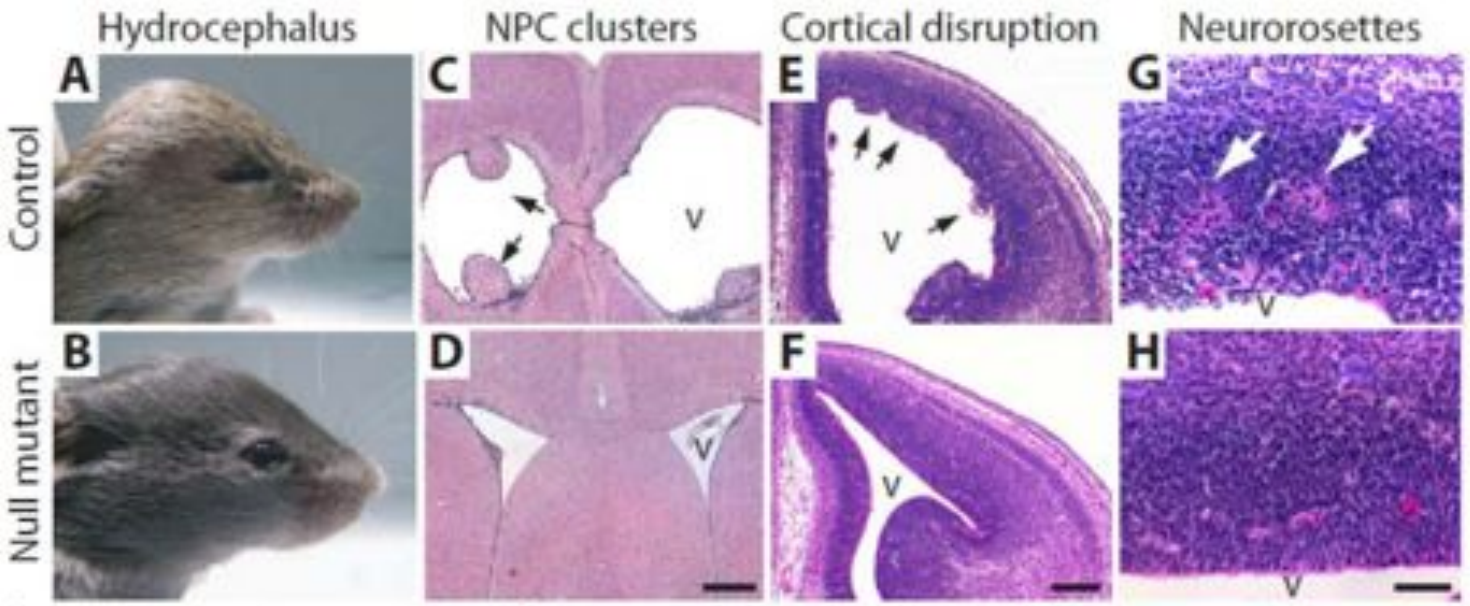


Figure 6 Lithium therapy rescues cell proliferation and hydrocephalus in *Bbs1*$^{M390R/M390R}$ mice. (a) Overview of the

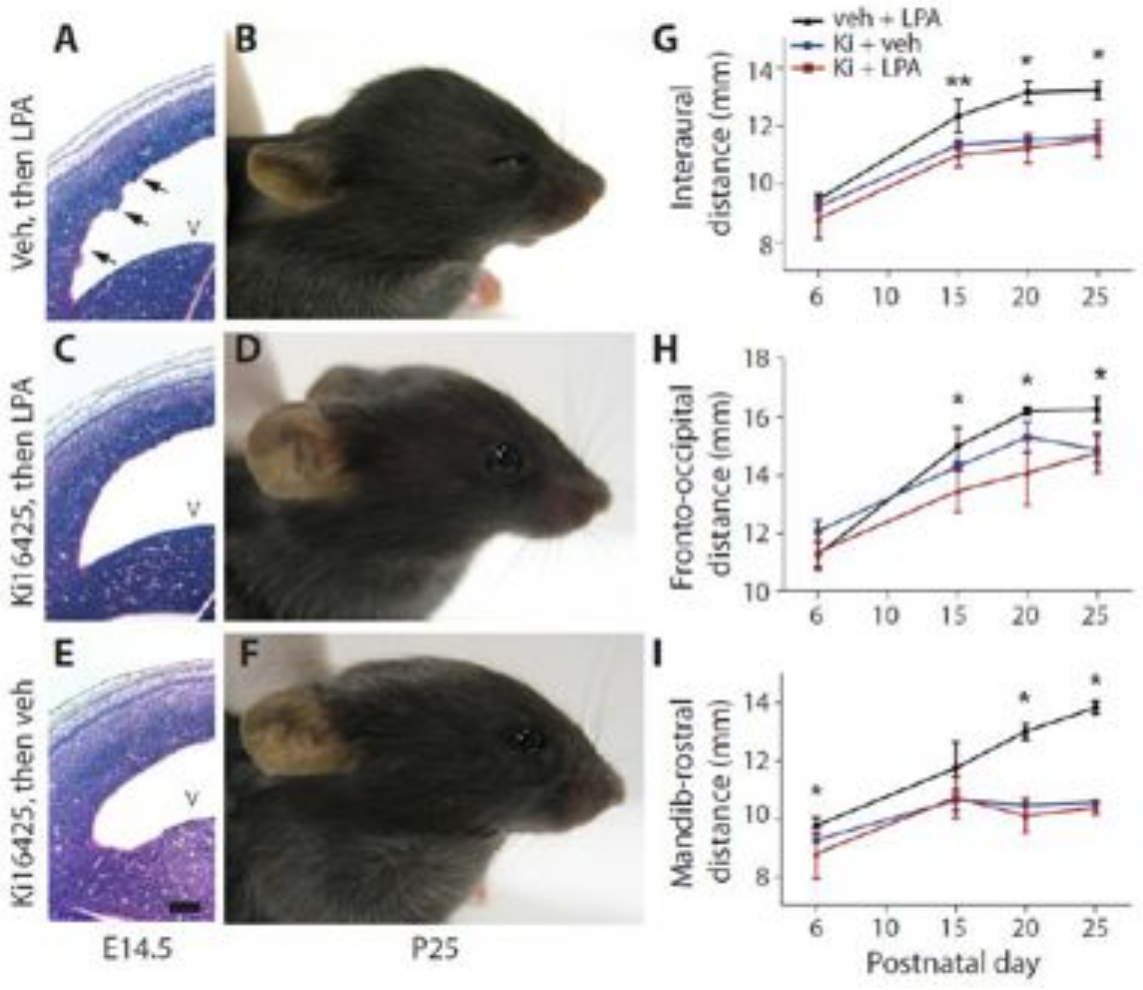
Histological Features of LPA-induced Fetal Hydrocephalus



- Loss of ependymal layer
- Exposure of subventricular zone and neuroprogenitor disruption
- Ependymal neurorosette and hetertopia formation
- Cilary defects
- 3rd ventricle occlusion and/or aqueductal stenosis

Pharmacological Prevention of LPA-induced Fetal Hydrocephalus

- Ki16425, a receptor antagonist with proven specificity against LPA1 and LPA3 was injected intraventricularly at E13.5 before LPA exposure
- Ependymal disruption and neurorosettes were diminished 1 day later
- Ventriculomegaly prevented at postnatal day 25



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fMRI vs Behavioral Assessments

Int. J. Devl Neuroscience 35 (2014) 7–15

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Kaolin-induced ventriculomegaly at weaning produces long-term learning, memory, and motor deficits in rats

Michael T. Williams[a,b,*], Amanda A. Braun[a,b], Robyn M. Amos-Kroohs[a,b], James P. McAllister II[c], Diana M. Lindquist[b,d], Francesco T. Mangano[b,e], Charles V. Vorhees[a,b], Weihong Yuan[b,d]

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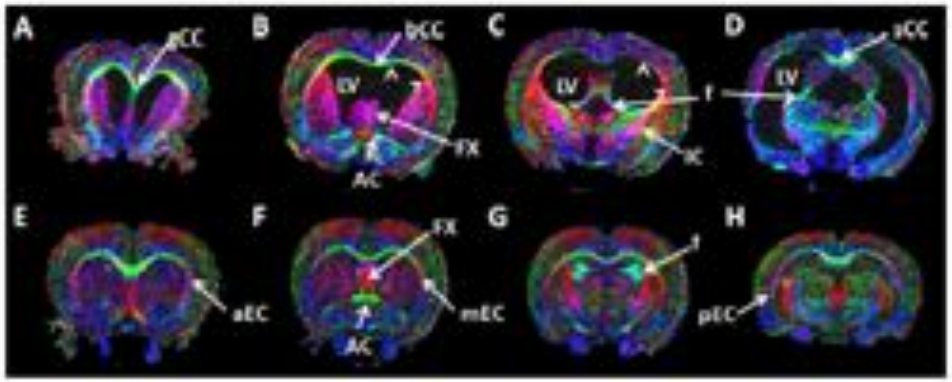
[e] Division of Pediatric Neurosurgery, Cincinnati Children's Research Foundation, Cincinnati, OH 45229, United States

DTI at 21d post-kaolin



Morris water maze at 28d post-kaolin by Evan's ratio (ER)

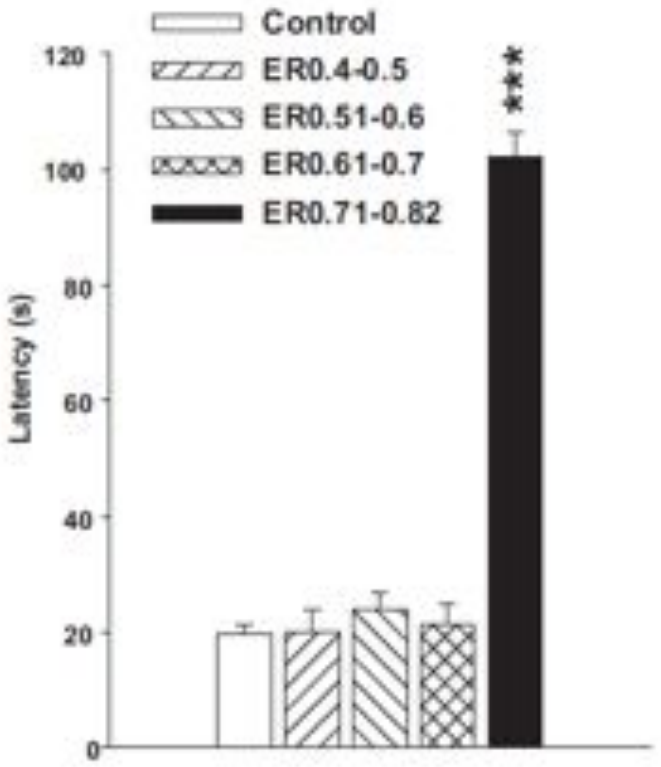
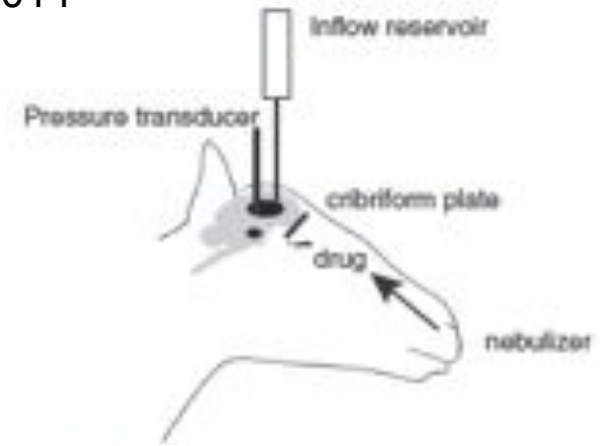


Fig. 7. Morris water maze cued platform was examined at least 1 h after the probe trial on P49. The ER0.71–0.82 animals were slower in locating the platform relative to the SAL animals ($p < 0.0001$). None of the other VM groups were different from the SAL animals. ***$p < 0.0001$, versus SAL.

Kim H, Moore SA, Johnston MG. Potential for intranasal drug delivery to alter cerebrospinal fluid outflow via the nasal turbinate lymphatics. *Fluids & Barriers of the CNS* epub 11(10), 2014

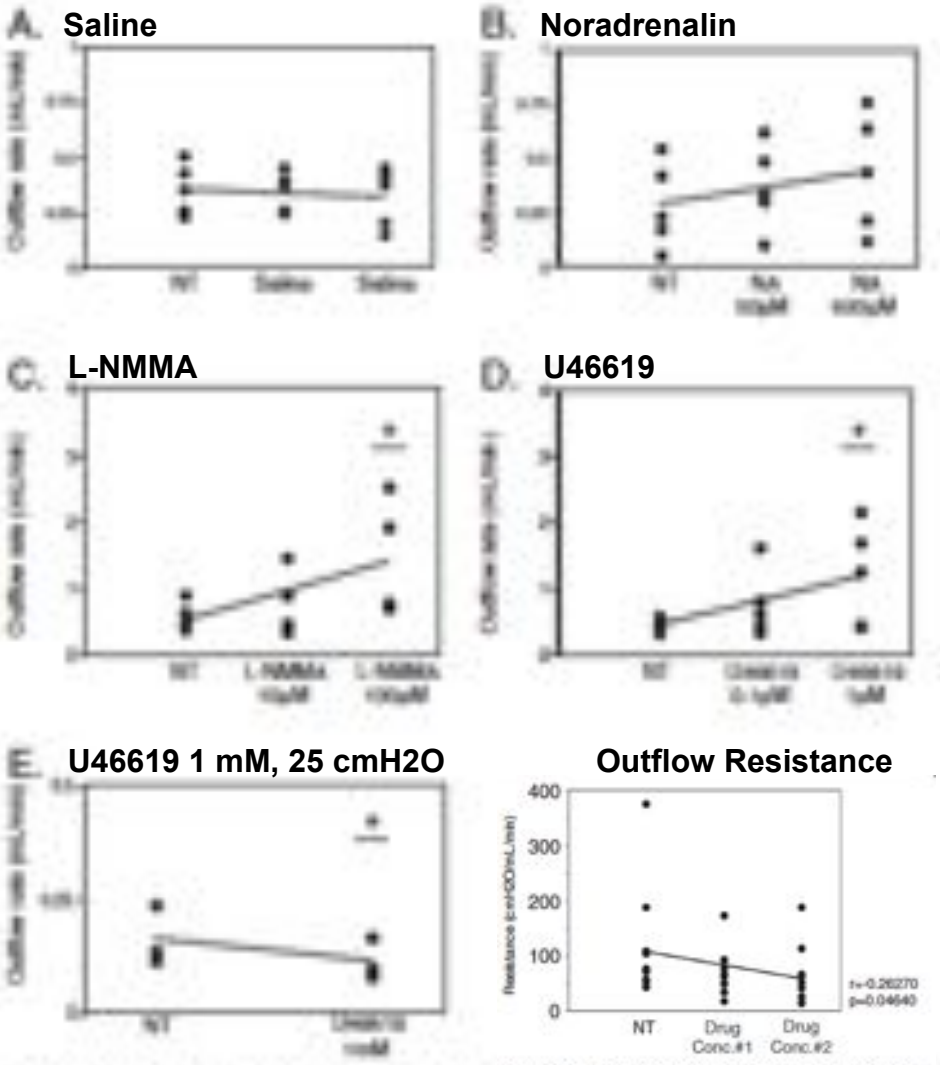


Lymphatic Flow

U46619 - thromboxane A2 analogue (increases or decreases)
= increased 2.44 fold

L-NMMA - NG-monomethyl L-arginine (NO inhibitor, inhibits lymphatic contractions)
= increased 2.29 fold

Noradrenalin (NA, increases or decreases)
= trend toward increase



Summary

- **Neuroimaging is essential for most animal studies**
  - **inherent variability and severity** – especially in adult vs pediatric (fixed vs expandable skull)
  - **regional differences** - ventricular volume better than Evan's ratio
  - **temporal progression** – slow usually becomes chronic
  - **treatment outcome** – shunting & pharmacological intervention
- **Need higher resolution**
- **Need cellular correlates of DTI**
- **Need non-invasive ICP measurements**
- **Need biomechanical and compliance studies**

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Many Thanks
To You and My Colleagues

Mark Wagshul, PhD

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Ann Logan, PhD

Hannah Botfield, PhD

Jack Walker, MD

Pat McAllister, PhD

Translating Time Across Species

	Rat	Mouse	Rabbit	Ferret	Cat	Macaque	Human
Gestation in days	G21	G19	G31	G41	G65	G165	G270
	Birth	Birth	G25	P2	G47	G85	G110
Corpus Callosum Appears	G18	G16	G21	G36	G39	G72	G91

Clancy B et al, Translating developmental time across mammalian species, *Neuroscience* 105: 7-17, 2001.
Clancy B et al, Web-based method for translating neurodevelopment from laboratory species to humans, *Neuroinformatics* 5:79-94, 2007. http://www.translatingtime.net