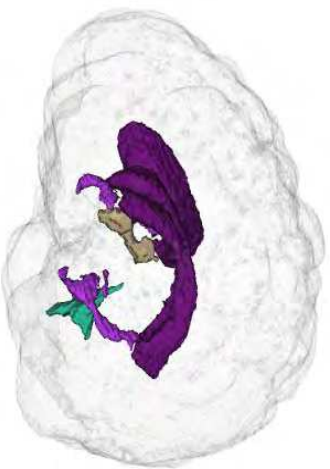
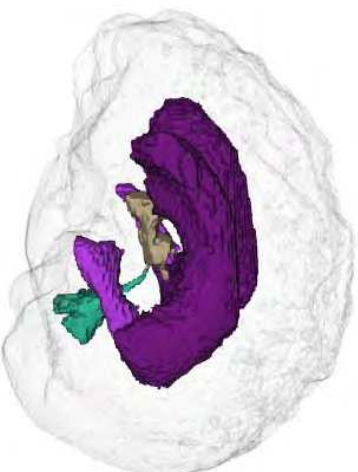
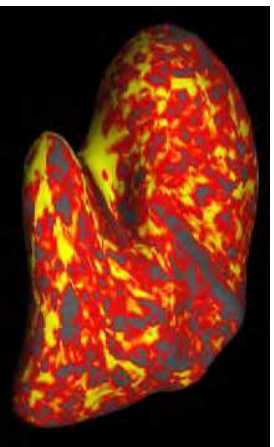


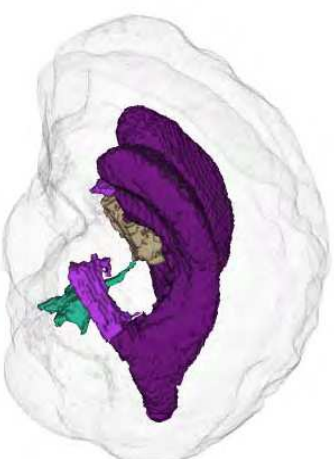
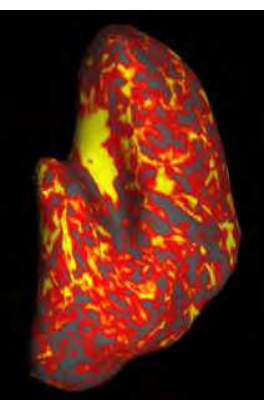
Quantitative MRI Techniques for Improved Differential Diagnosis and Treatment of NPH



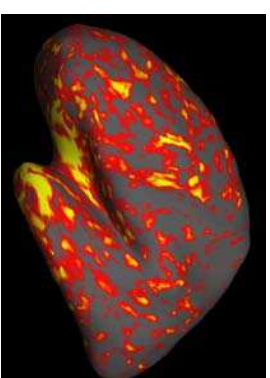
Normal



NPH



Alzheimer's



Norman Relkin MD, PhD
Weill Cornell Medical College
New York, NY

Objectives

- Review current imaging practices for hydrocephalus diagnosis and management
- Describe quantitative MRI techniques that can be used to improve NPH diagnosis
- Demonstrate application of quantitative MRI imaging to the development of pharmacotherapy for NPH

Clinical Roles of Neuroimaging in Hydrocephalus

- Recognition and Differential Diagnosis
- Prognostication of Treatment Response
- Management post Treatment
- Outcome Assessment

Roles of Imaging in Hydrocephalus Diagnosis

Use	Aim	Modality
Primary Diagnosis	Document ventriculomegaly	MRI, CT, Ultrasound*
Distinguish communicating from non-communicating hydrocephalus	Document presence or absence of obstruction to CSF flow	MRI, CT, Ultrasound*
Supportive Diagnosis	Associated features eg: increased subarachnoid space, sulcal effacement, etc	MRI, CT, Ultrasound*
Physiologic Characterization	Document abnormal CSF flow	Proton density MRI, Phase Contrast MRI, Cisternography

* Ultrasound used exclusively in Infants prior to fontanelle closure

Uses of Imaging in Hydrocephalus Therapeutics

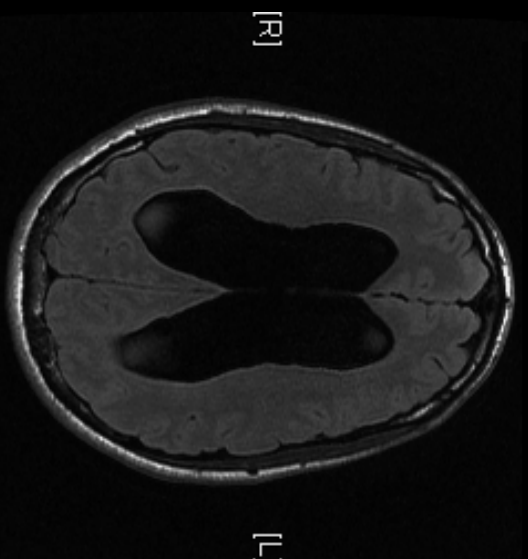
Use	Modality
Guide LP or Lumbar Drain placement	X-ray, Fluoroscopy
Confirm Shunt Placement, Valve setting, shunt Integrity	X-ray, CT, (MRI)
Monitor Ventricular Size (Shunt failure, Overdrainage)	CT (MRI), Ultrasound*
Identify Post-shunt Complications (eg: subdurals)	CT (MRI), Ultrasound*

* Ultrasound used exclusively in Infants prior to fontanelle closure

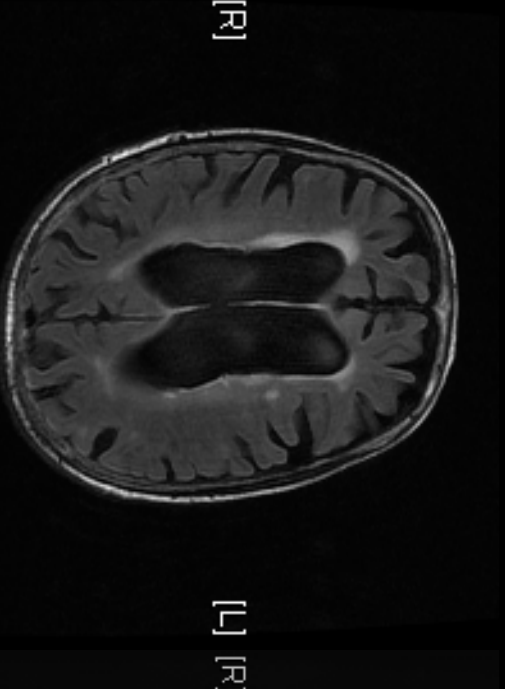
The Challenge of Diagnosis of Adult Hydrocephalus:

Judging whether Ventricular enlargement is disproportionate to cerebral atrophy

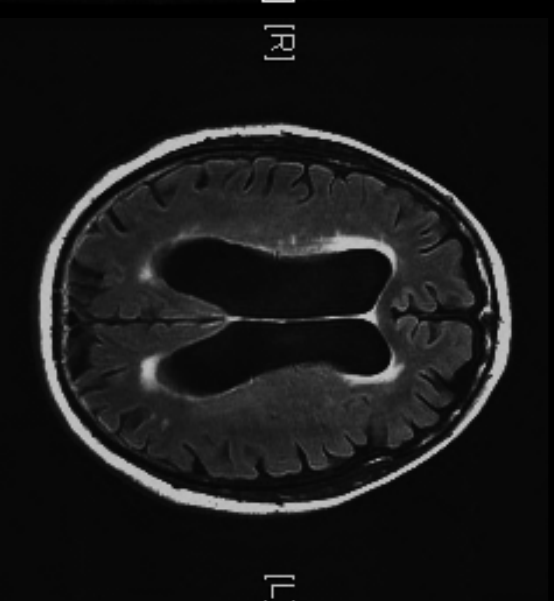
A



B



C



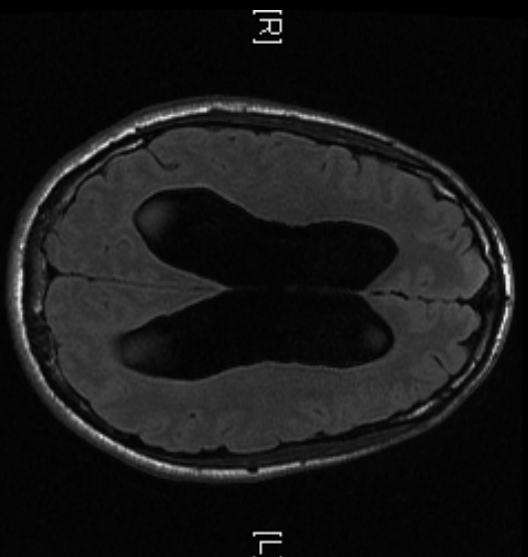
T2 FLAIR Images

Which patients have hydrocephalus?

The Challenge of Diagnosis of Adult Hydrocephalus:

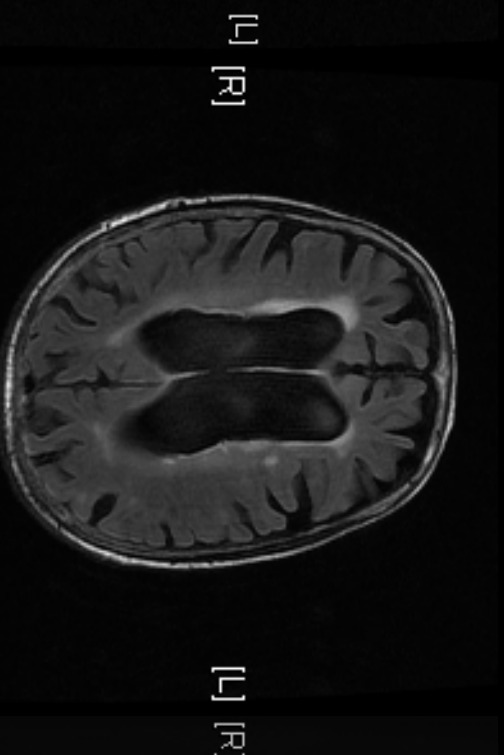
Judging whether Ventricular enlargement is disproportionate to cerebral atrophy

A



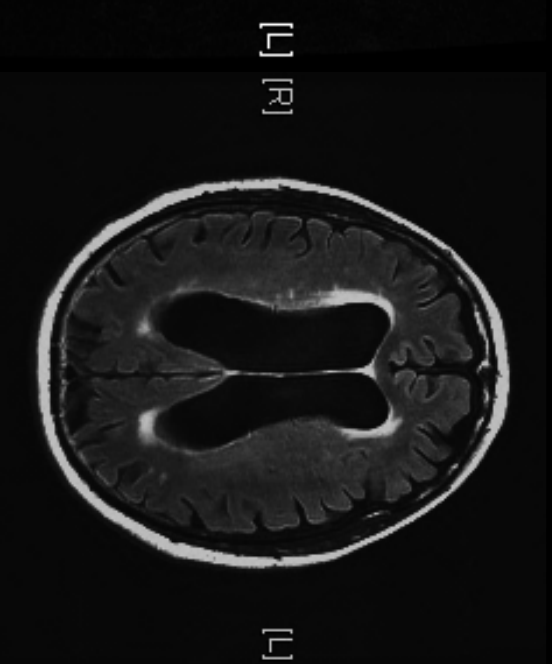
35 year old
with Aqueductal
Stenosis

B



79 year old
with Alzheimer's
Disease

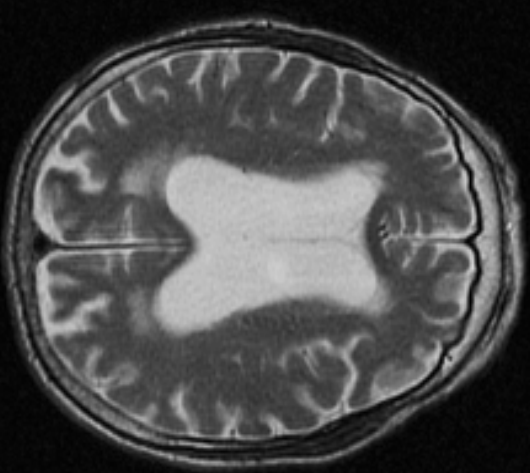
C



87 year old
with Shunt responsive
Normal Pressure
Hydrocephalus

T2 FLAIR Images

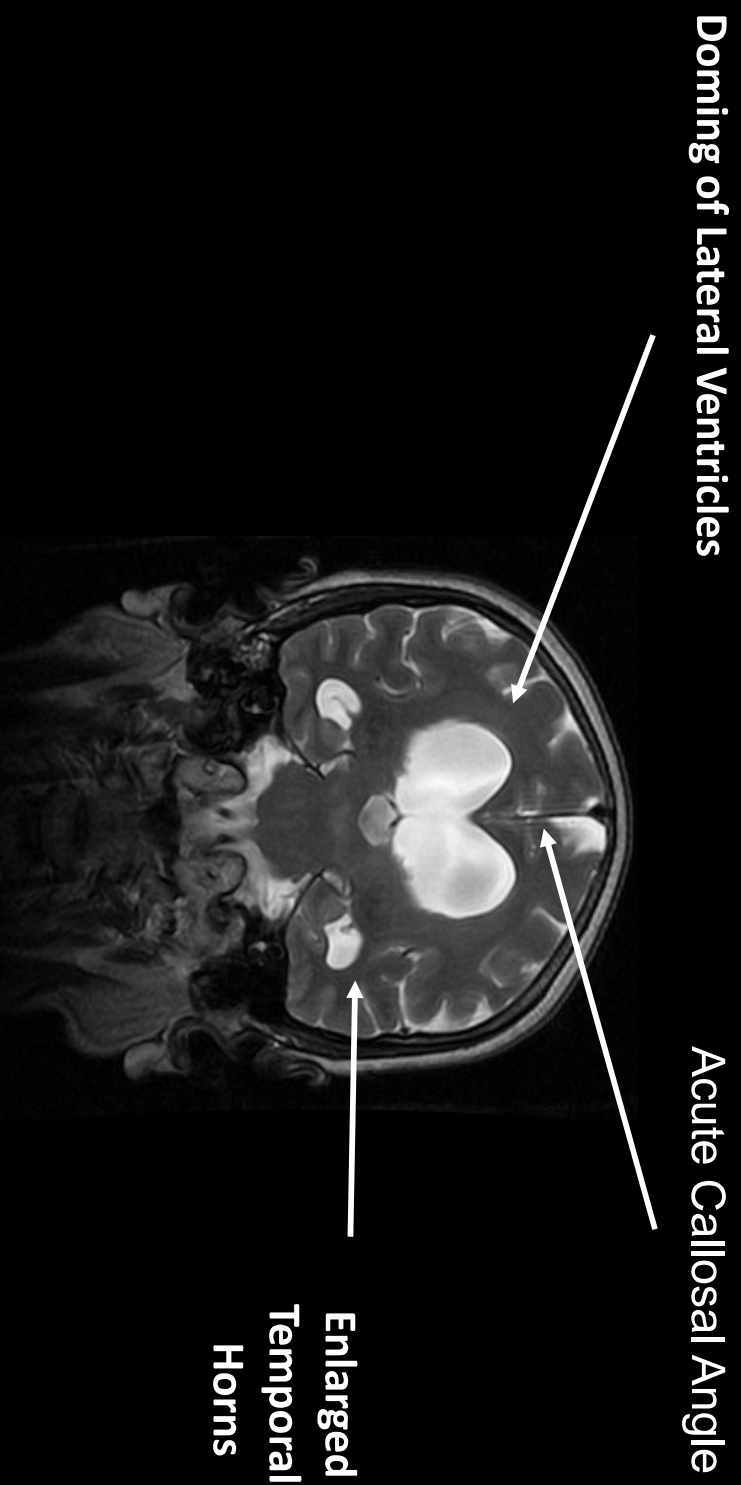
The Radiologist's Hedge



“The lateral ventricles are enlarged relative to age. This could be a consequence of central atrophy or an element of communicating hydrocephalus may be present...”

- MRI clinical report

Ventricles are symmetrically enlarged in NPH

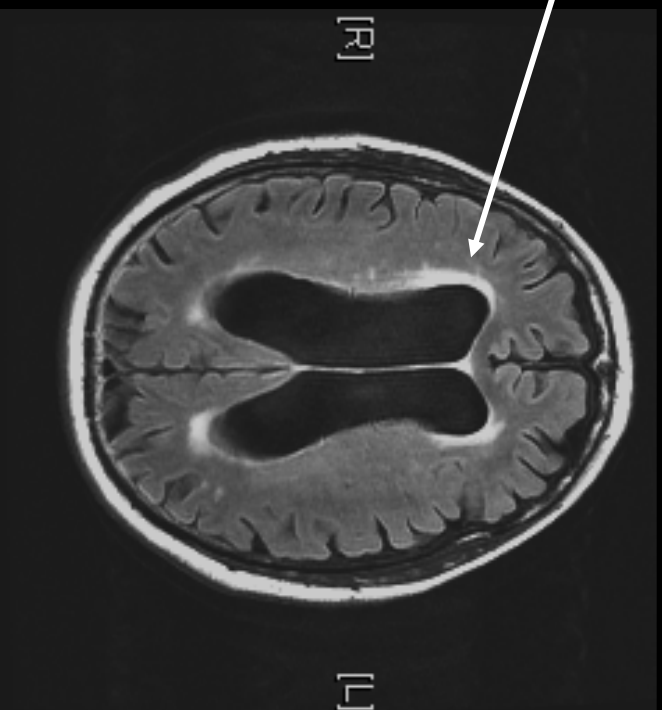


- Asymmetric enlargement suggests another process: e.g.: cerebrovascular disease, trauma, developmental anomaly, etc

Caveat: Ex vacuo (atrophy-related) ventricular enlargement also symmetric

Transependymal CSF Flow is Increased in NPH

“Capping”

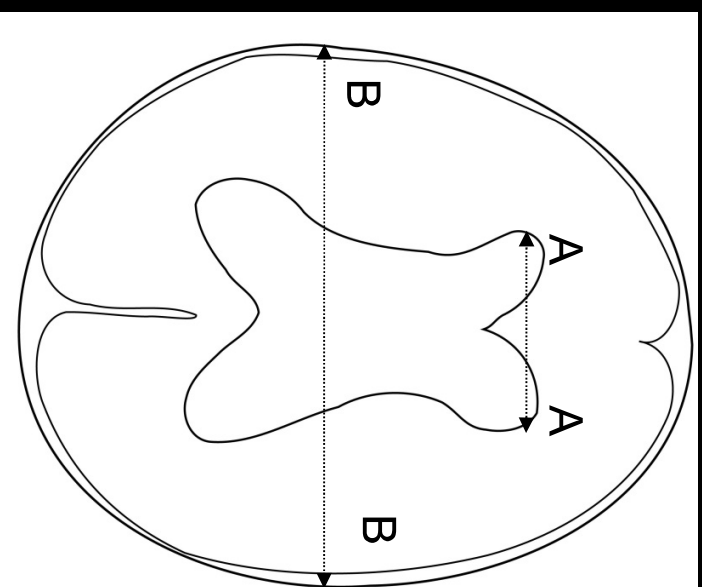
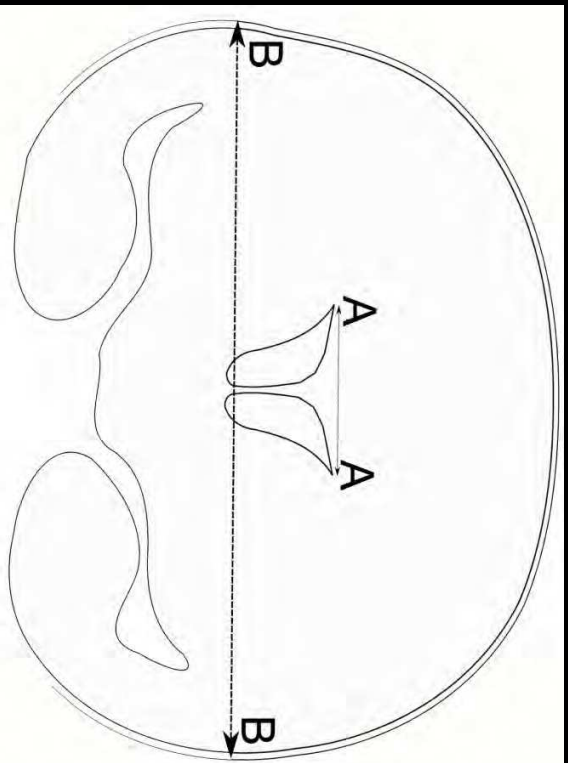


AXL T2 FLAIR

- Caveat: Reverse transependymal flow can be difficult to distinguish from periventricular ischemic changes

The Evan's Index = $A \div B$

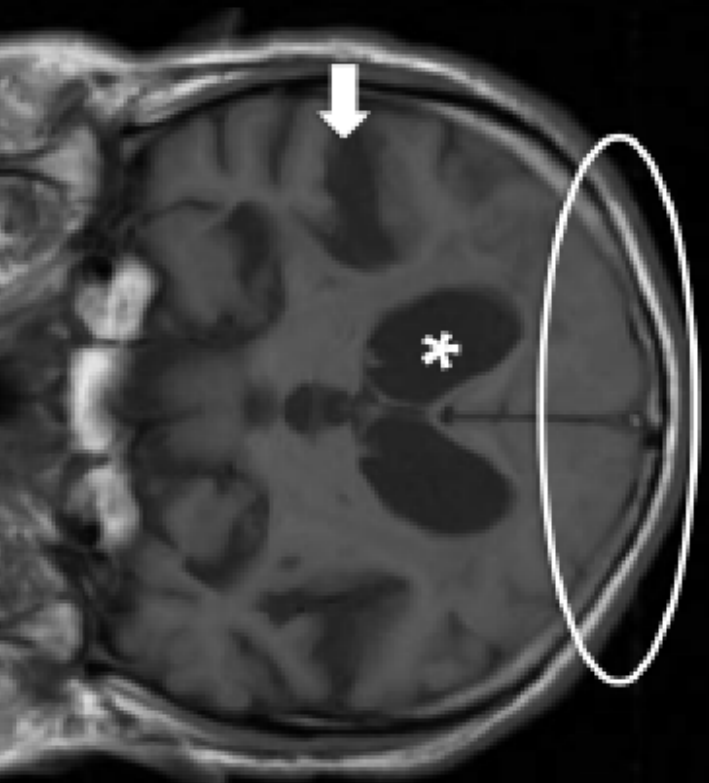
Ratio of diameter of anterior horns of lateral ventricle to intracranial diameter



- Diagnostic criteria for Idiopathic NPH require an Evan's Index of 0.3 or greater
- Caveat: Evan's Index may be elevated to a comparable degree from age-related cerebral atrophy

DESH: Disproportionately Enlarged Subarachnoid Space Hydrocephalus

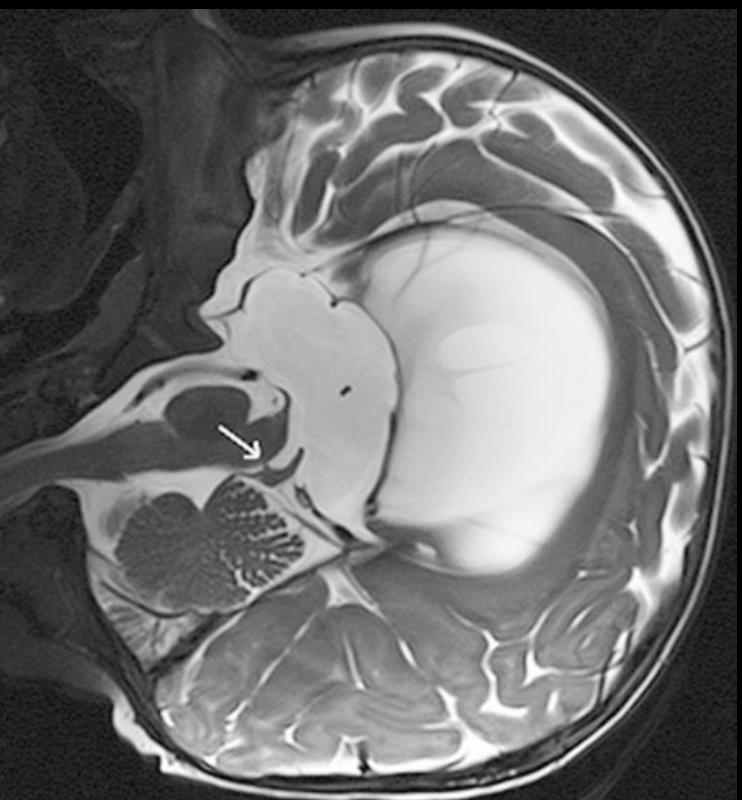
A useful radiologic finding in the diagnosis of iNPH



Circles: fronto-parietal convexity sulcal effacement and sagittal sinus abutment
Arrows: Enlargement and upward displacement of roof of Sylvian fissure

Steady State Free Precession MRI techniques (e.g.: FLESTA, 3D-CISS) reveals anatomic obstructions in Aqueductal Stenosis

FLESTA = fast imaging employing steady state acquisition (GE)
3D-CISS = constructive interference in steady state (Siemens)



- Aqueductal web (arrow) visualized by high resolution FLESTA MRI

Image from Parekh & Prabhu (2010) Pediatric Radiology S154)

Advanced MRI Imaging Protocol for NPH

Quantitative MRI measurements can supplement conventional clinical sequences in patients suspected of having NPH:



Volumetric MRI

Cortical Shrinkage
Ventricular Enlargement



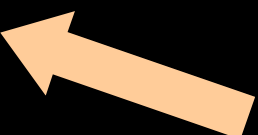
Phase Contrast Imaging

Pulsatile CSF Flow
CSF Production
MR-ICP



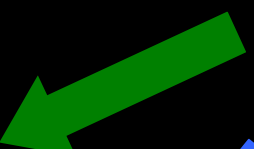
Diffusion Tensor Imaging

Fractional Anisotropy
Quantitative Diffusion Tensor

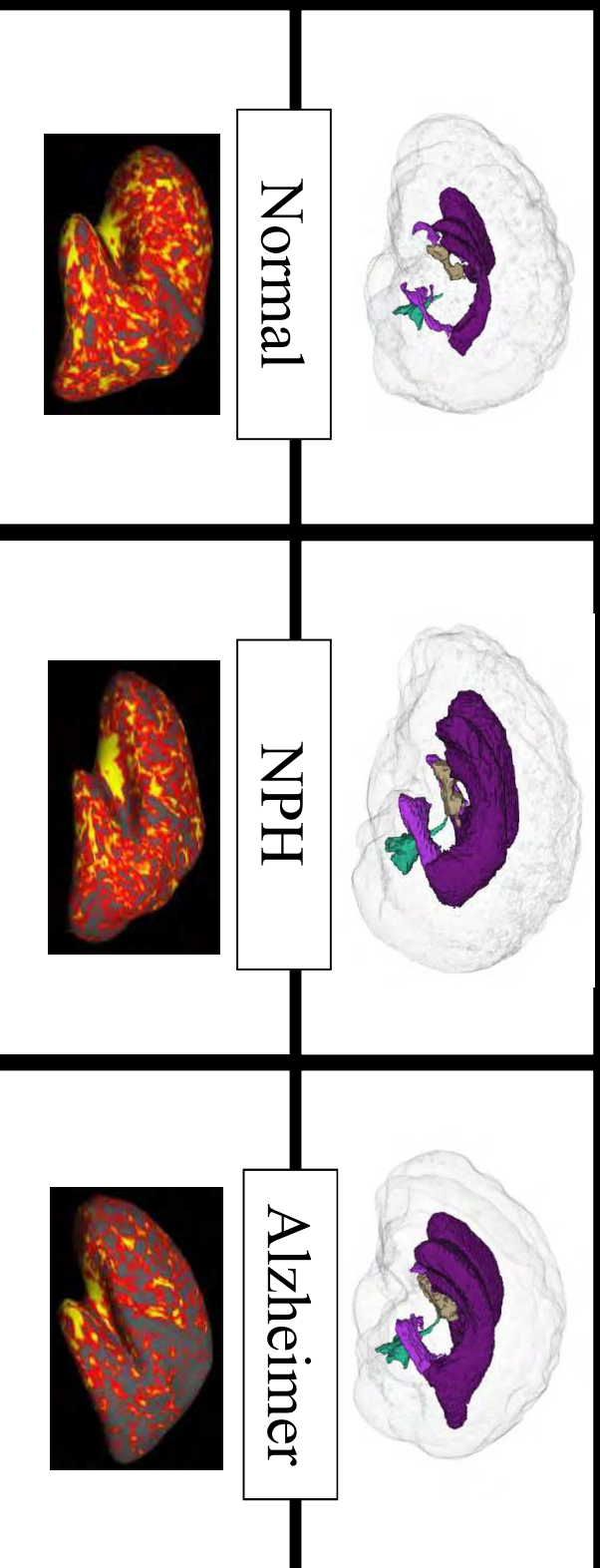


Arterial Spin Label

Cerebral Blood Flow



Volumetric MRI for NPH Differential Diagnosis



= Ventricular Volume Maps



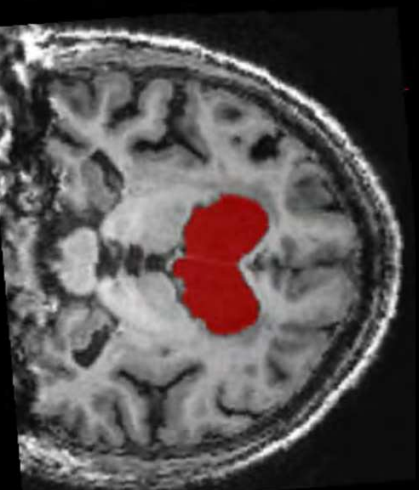
0mm 1.5mm 3.5mm
= Cortical Thickness Maps

- Quantitative analysis can extract more information from MRIs than can be obtained by visual inspection alone
- Quantitative studies require 3D isotropic pulse sequences (e.g: 3D-BRAVO, MP-RAGE) and more acquisition stringency than standard clinical scans

MRI Volumetrics:

Ventricular Volume Determination

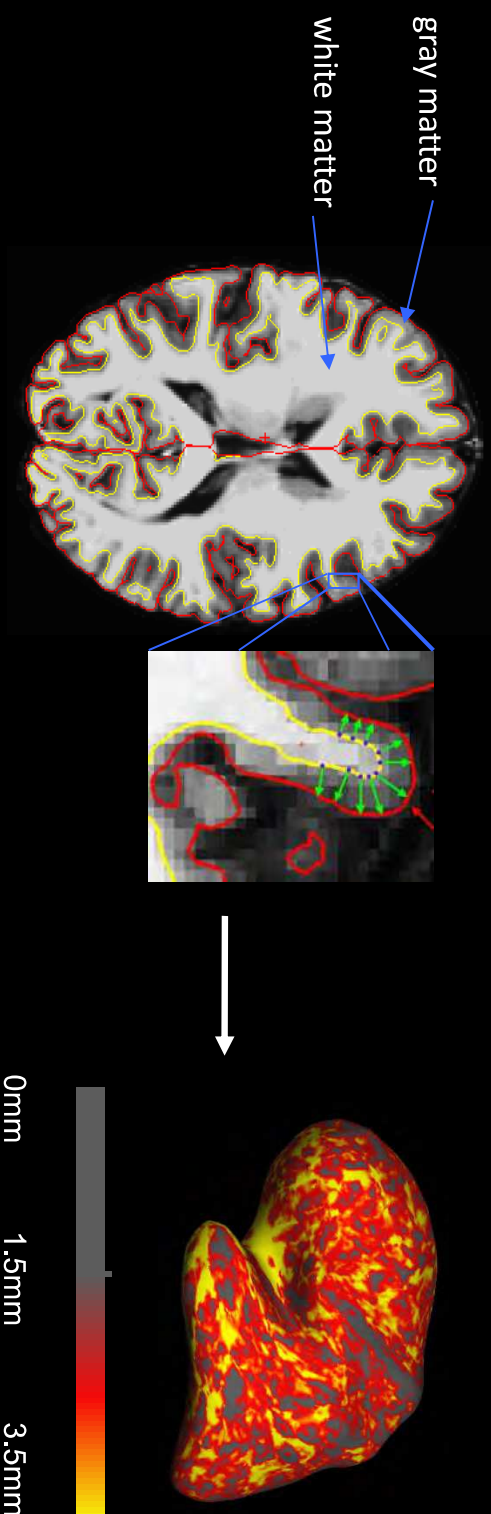
- Fully automated segmentation software is available for measuring ventricular volume in 4 dimensions but often fails to correctly segment the very enlarged ventricles that occur in association with NPH



- At the present time, semi-automated programs such as Brain Ventricular Quantification (“BVQ”) that use a region-growing method based on operator-selected seed points have provided the best performance in quantifying volumes of enlarged ventricles.

MRI Volumetrics: Cortical Thickness Measurements

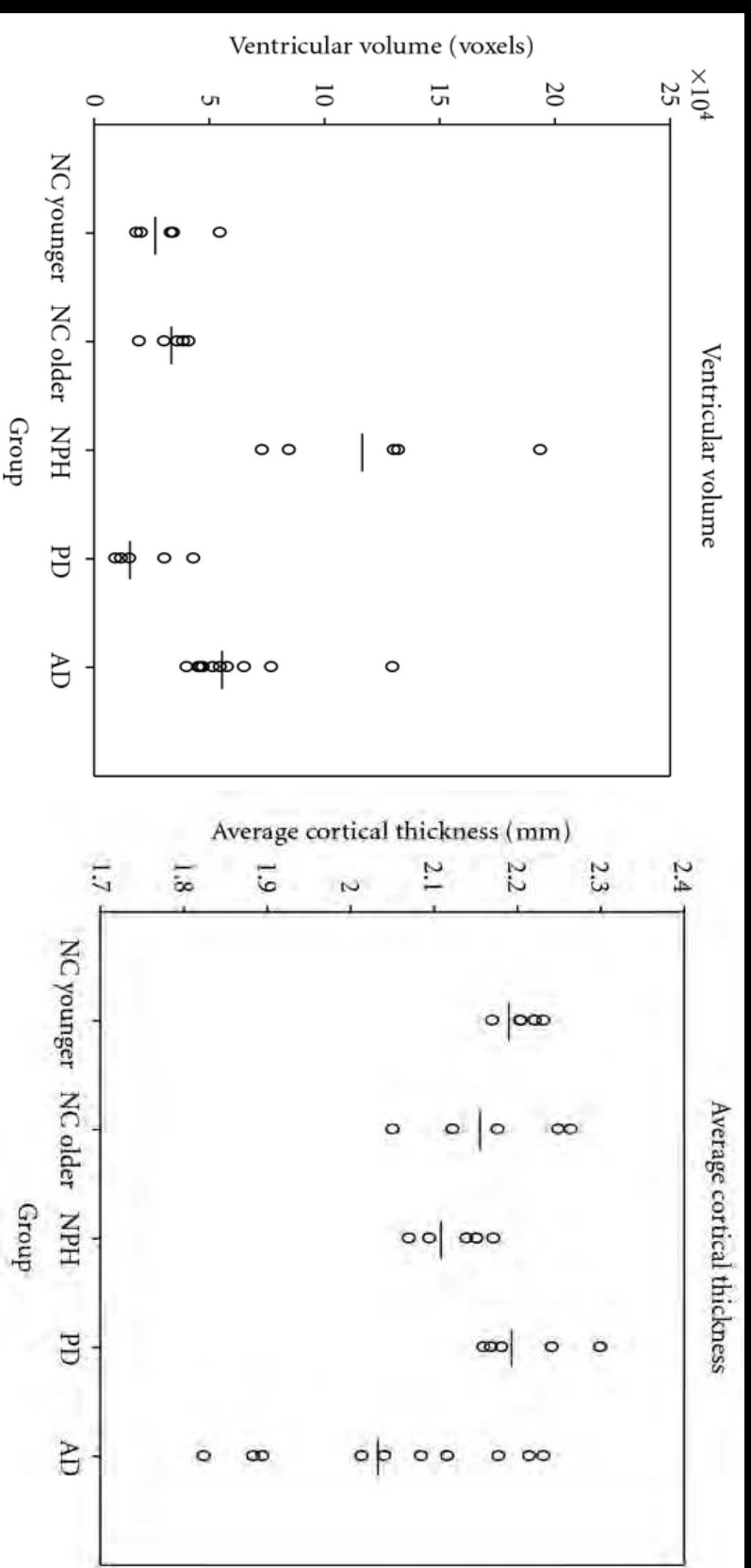
- Cortical thickness measurements provide an index of cortical atrophy and may be more refractory to artifactual distortion in the context of ventriculomegaly than regional brain volume measurements (eg hippocampal volume)



The freeware program FreeSurfer measures the thickness of cerebral cortex by determining the distance between the gray and white matter boundaries.

Cortical Thickness can be mapped across the entire surface of the brain.

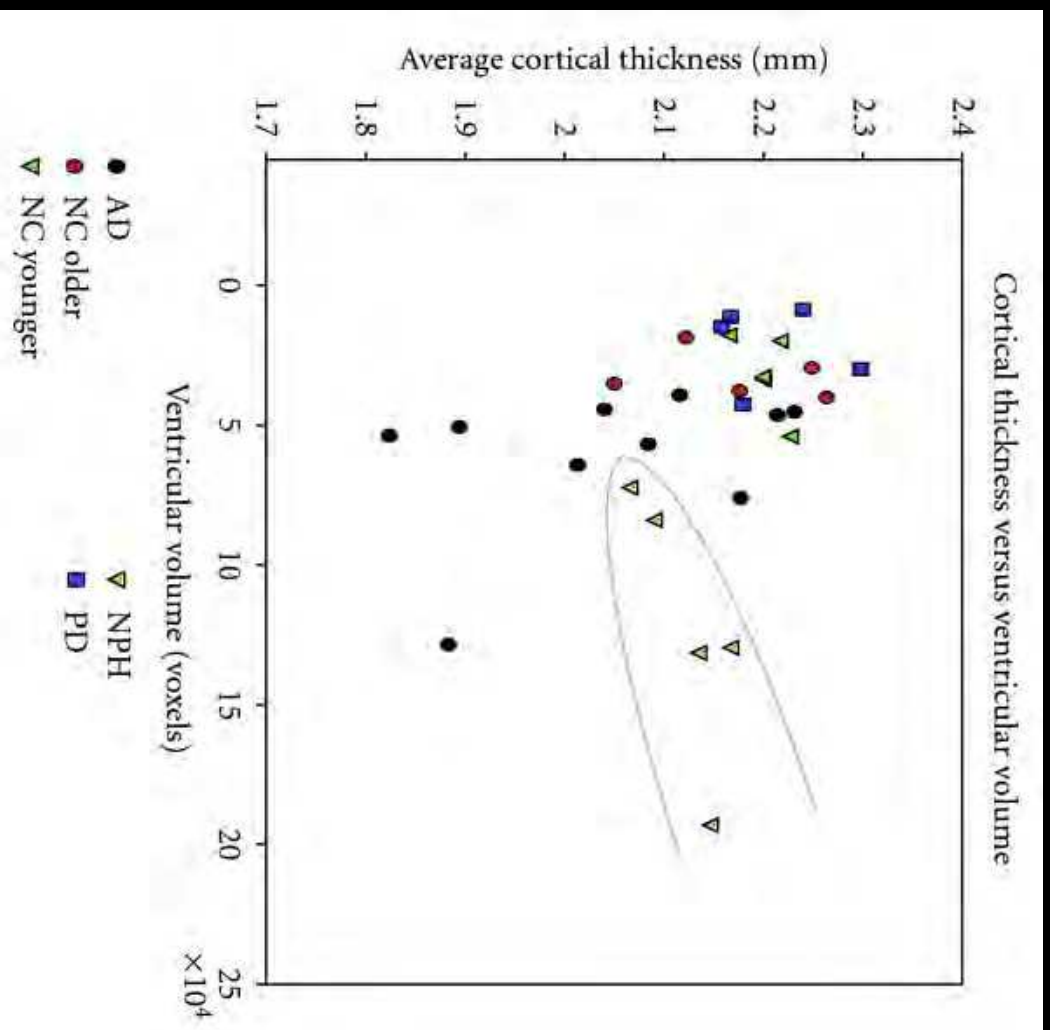
Ventricular Volume and Cortical Thickness in NPH



Neither ventricular volume nor cortical thickness measurements alone distinguish iNPH cases from Alzheimer's disease

From Moore D, et al (2012) *Neurol Res Int*.

Combined Ventricular Volume & Cortical Thickness Measurements better distinguish iNPH from other disorders



From Moore D, et al (2012) *Neurol Res Int.*

Shunt responsive NPH associated with increased Aqueductal CSF flow

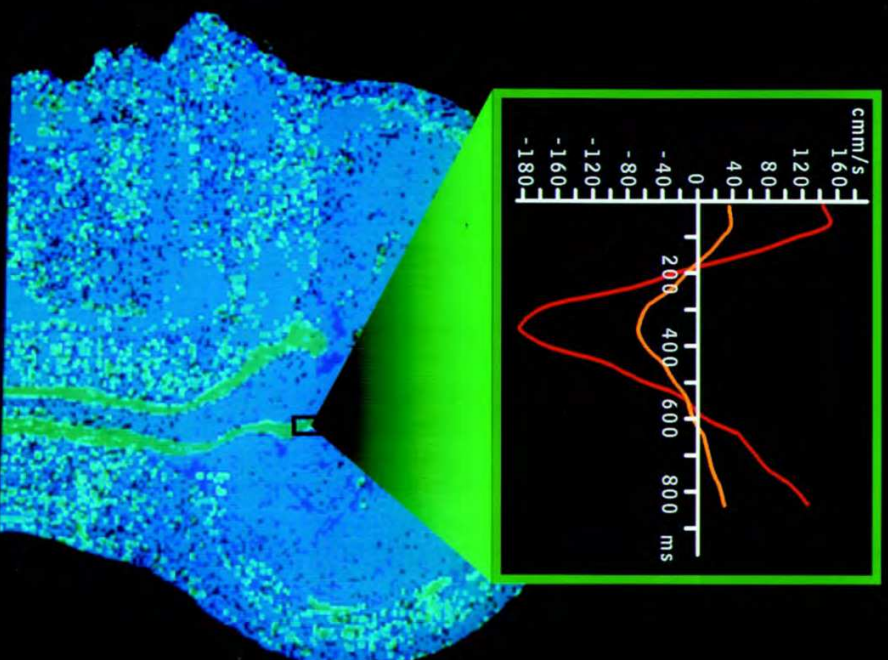


Image from Bradley, W (1999) J Neuropsychiatry

Measurement of Cerebrospinal Fluid Flow at the Cerebral
Aqueduct by Use of Phase-contrast Magnetic Resonance
Imaging: Technique Validation and Utility in Diagnosing
Idiopathic Normal Pressure Hydrocephalus

Neurosurgery, Vol. 50, No. 3, March 2002

Patrick Luetmer, et al, Mayo Clinic, Rochester, Minnesota

- 236 patients studied including NPH and controls
- The average flow rate in NPH was 27.4 +/- 15.3 ml/min
- The average flow rate in normals / non-NPH was 8.47 +/- 4.23 ml/min
- **CONCLUSION:** CSF flow measurements of less than 18 ml/min with a sinusoidal flow pattern are normal. CSF flow of greater than 18 ml/min suggests idiopathic NPH.

Caveat: Phase Contrast flow measurements vary across scanner platforms

Can Imaging Guide Development of Pharmacologic Treatments for NPH ?

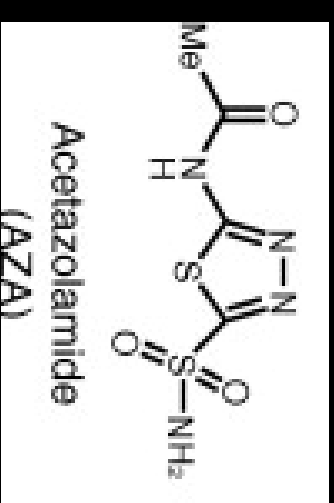
- Current surgical treatments work by increasing CSF clearance
- Over the past decade, Phase Contrast MRI studies of iNPH have revealed increased aqueductal CSF flow (Bradley, Scalloto) and signs of excessive CSF production (Bateman).
- Diffusion tensor studies have provided evidence of increased interstitial brain water content, particularly in white matter (Ng, Kano, Lendfeldt, Ivkovic)
- These results suggest that pharmacologic interventions that reduce CSF production and interstitial edema could prove useful for treating iNPH

A pilot study of MRI Guided Pharmacotherapy for NPH

N Relkin, N Alperin, H Katzen, et al (AAN 2012)

- Recent advances in MRI methodology have created a powerful new platform for exploring the structural and hydrodynamic changes in the brain associated with NPH and its treatment
- We initiated a pilot study to examine the feasibility of using clinical and quantitative MRI measures to evaluate a potential drug treatment for iNPH
- An initial open label experience involved administering acetazolamide (ACZ) to 5 iNPH patients who consented to serial quantitative MRIs

Can Acetazolamide (ACZ) be used to treat iNPH?



- Acetazolamide (ACZ) is an established treatment for idiopathic intracranial hypertension (IIH), high altitude cerebral edema and other disorders
- ACZ is not accepted for use in iNPH and has never been formally tested in prospective, randomized clinical trials
- Two retrospective case series (Almard 1990, Garcia-Gasco 2005) involving a total of 16 NPH patients found ACZ (250-500mg/day) reduced symptoms sufficient to avoid a shunt for a year or longer

MRI Feasibility Study Methods: Patient selection

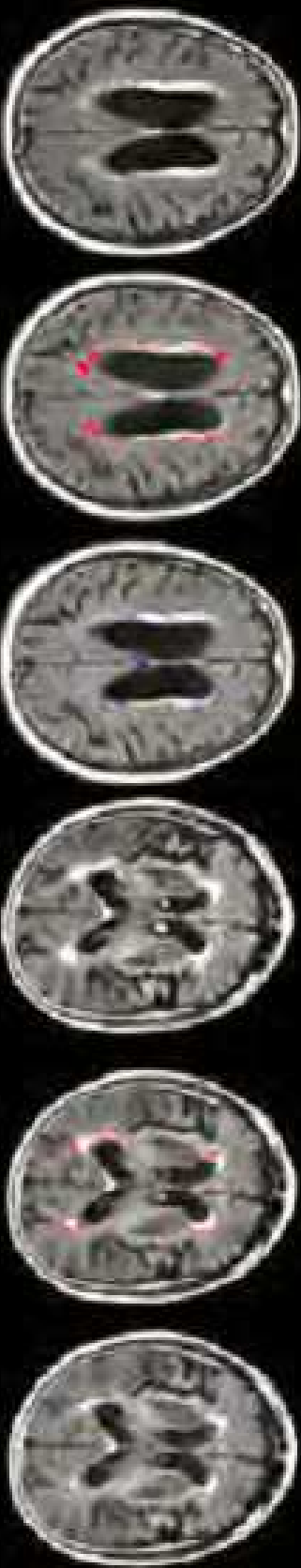
- Patients with Probable iNPH of mild severity who did not require immediate neurosurgical intervention
- T1-weighted MRI evidence of transependymal CSF accumulation, Phase Contrast evidence of Increased CSF flow and DTL evidence of abnormal mean diffusivity
- No contra-indications to acetazolamide treatment or MRI

MRI Feasibility Study Results

Cohort Characteristics

- 3 Male, 2 Female
- Mean Age 81.4 (Range 73-91)
- Mean CSF Flow Rate: 17.1 (Range 13.9-25.8)
- Mean Baseline Boon Gait Score: 11.4 (Range 8-17)

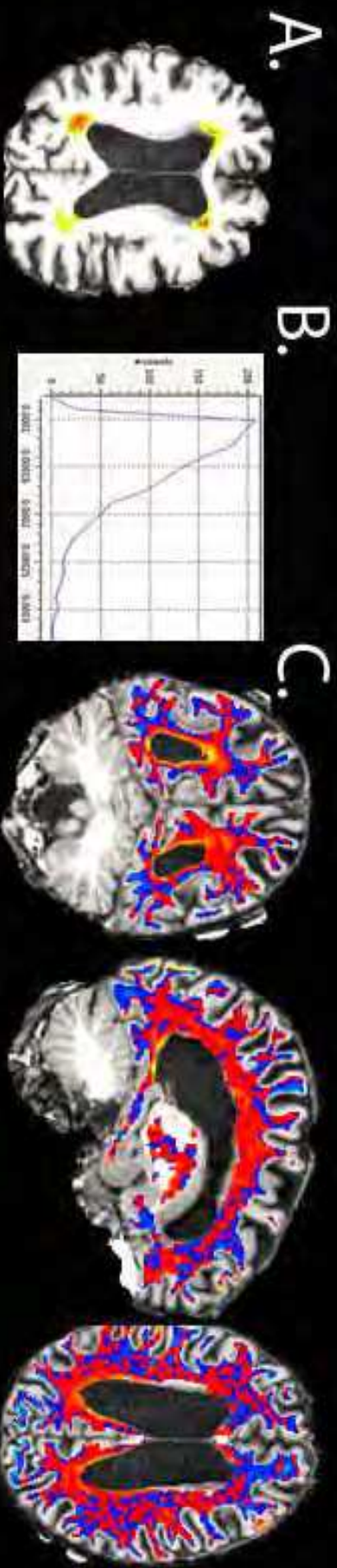
Volume of White Matter Hyperintensities decreases after Acetazolamide treatment



	Subject 1			Subject 2		
	Baseline	ACZ 125mg/d	ACZ 250mg/d	Baseline	ACZ 125mg/d	ACZ 250mg/d
WMH (mls)	24.5	18.8	16.7	19.4	14.6	13.5
Cumulative WMH change		-23%	-34%		-25%	-32.5%
Bacon Gait Score	17	12	12	8	6	4
Cumulative Bacon change		-29%	-29%		-25%	-50%

MRI Feasibility Study Results

Diffusion Tensor Outcomes



A) T1 hyperintensities from NPH patient treated with 125mg/d ACZ for 1 month. Within these regions, MD decreased a maximum of 8.7% and the isotropic (free water) fraction decreased by maximum of 5.7% after ACZ

B) Histogram showing number of voxel (y-axis) with decreased Mean Diffusivity (x axis) after ACZ.

C) Free water fraction after ACZ. Red zones: pixels with decrease free water after ACZ treatment blue zones have increased free water fraction

Primary Clinical Outcome

- Boon Gait Scale – 38 point scale (2-40) with lower scores indicating a better gait performance
- A 3 point change is considered clinically significant

4 of 5 subjects showed improvement on the Boon after 1 month at 125mg/day and 4 of 5 showed further improvement with dose escalation to 250mg

Mean Gait Score

Pre-treatment: 11.4

Post 125mg ACZ: 7.75

Post 250mg ACZ: 6.5

Conclusions

- Neuroimaging is essential to the diagnosis of NPH and plays an increasingly important role in guiding treatment
- Visual inspection of conventional clinical images can assist in diagnosis but is a subjective process with limited power to distinguishing NPH from other conditions
- Quantitative MRI techniques are advancing our understanding of the pathophysiology of NPH and are likely to transform clinical diagnosis, prognostication and treatment in the future.

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Milos Ivkovic, Ph.D.,-2

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