USC University of Southern California

# TIMESLIP in Normal Pressure Hydrocephalus, Dementia, CSF & Interstitial Glymphatic Flow

Wende Gibbs, MD, Department of Neuroradiology
Meng Law, MD, MBBS, Department of Neuroradiology

University of Southern California, Keck School of Medicine

Jeffrey A. Bennett, MD University of Florida

University of Florida Health

## Vascular Constributions to AD @ USC

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NIH R21 EB012456 01A1 (Law)
NIH 1ULRR031986-01 (Law)
NIH NIA P01-AG123435 (Chui)
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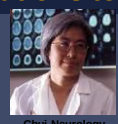

Chui Neurology


Zlokovic Zilkha Cell Biology


Schneider Psychiatry


Brinton Pharmacology


Thompson & Toga INI


Caleb Finch Gerontology

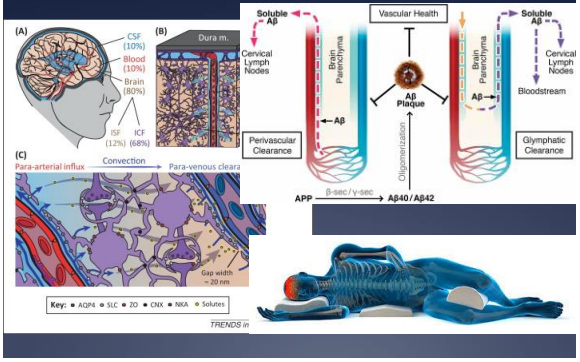
## Outline

- Hypothesis: BBB, Brain Perfusion, Glymphatics & Brain Compliance
  - Everything gets smaller and worse as you get older (Bill Bradley)
- Abnormal BBB DCE MRI in MCI and AD
  - Correlation with CSF markers and CSF flow (Zlokovic, Law, Chui et al)
- What is Normal flow of CSF and ISF?
  - Bulk flow ?
  - Pulsatile flow ? Diffusion Flow
  - Drainage of CSF – Relative contributions unknown from
    - Arachnoid granulations
    - Perineural nerve sheaths
    - Drainage into the dural lymphatics/glymphatics then neck
- Cine Phase Contrast & Time Slip Spin Imaging of CSF Flow

## Vascular – Alzheimer – NPH Spectrum

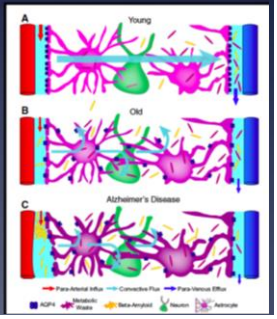
- Hypothesis: BBB, Brain Perfusion, Glymphatics & Brain Compliance
  - Everything decreases or gets worse as you get older
- Considerable overlap between 3 dementia phenotypes
- Aging and Vascular Risk Factors Contributions to Brain Aging
- Decreased Blood Flow, Glymphatic Drainage of Amyloid – Tau – AD
- Decreased Brain Compliance of BOTH ISF and CSF flow - NPH
- **THAT IS these ARE the same diseases along the dementia spectrum**

## Vascular vs Glymphatic vs Compliance

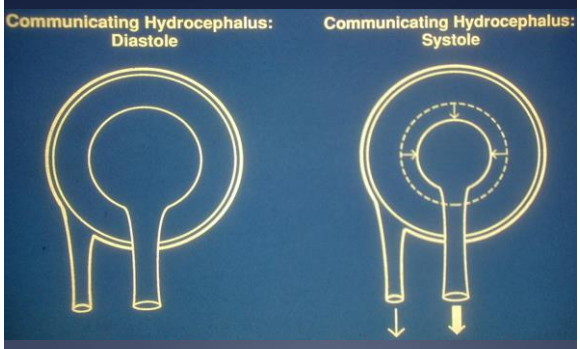



## Glymphatic dysfunction: Aging

- In aged mice, 80-90% reduction in glymphatic function
- Depolarization correlates with CSF-ISF exchange, suggesting glymphatic dysfunction partly due to dysregulation of astroglial water transport
- Additional contributing factors include:
  - 66% decline in CSF production
  - 27% decline in CSF pressure
  - Arterial wall stiffening → reduction in arterial pulsatility



**Courtesy Bradley WG**, et al "Radiology 178:459-466, 1991




**Aging: Decreased Perfusion, Decreased Lymphatics, Decreased Compliance**

## CSF Flow – pulsatile/diffusion Not bulk flow like blood vessels

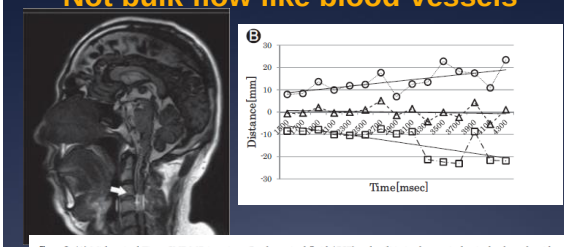
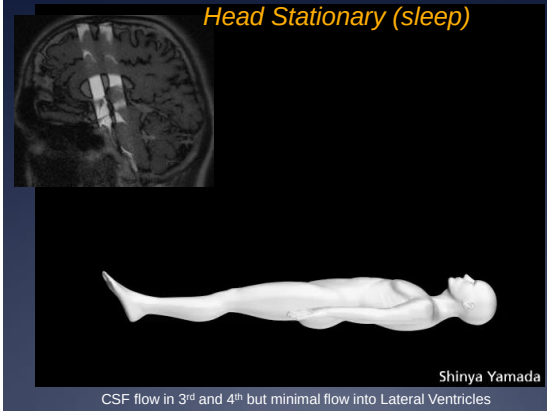



**Figure 9** (A) Mid sagittal Time-SLIP MR imaging. Cerebrospinal fluid (CSF) pulsatility in the cervical spinal subarachnoid space were traced by semiautomated tracing software (arrow). (B) Graph showing the distance traveled by the CSF over time. The open circles and the open squares indicate the upper and lower position of labeled CSF, respectively. The open triangles indicate the average of the upper and lower positions. Note that CSF had spread out by the time of observation and no unidirectional bulk CSF flow was observed. Reprinted with permission fromYamada.[7]

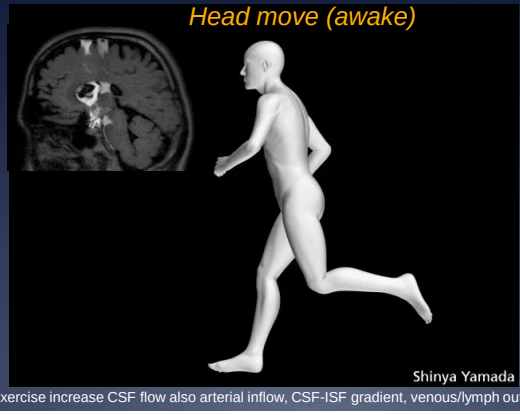
- Yamada S & Kelly E Seminars in US, CT and MRI 2016

## Head Stationary (sleep)




CSF flow in 3rd and 4th but minimal flow into Lateral Ventricles

## Head move (awake)




Exercise increase CSF flow also arterial inflow, CSF-ISF gradient, venous/lymph outflow

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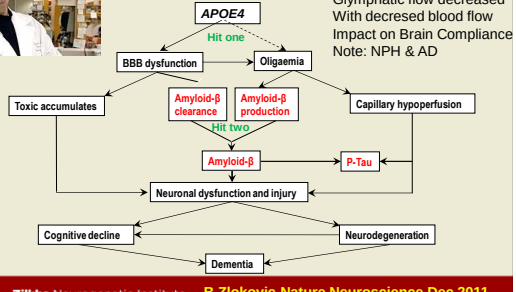
## The two-hit vascular hypothesis for Alzheimer's disease




Glymphatic flow decreased
With decresed blood flow
Impact on Brain Compliance
Note: NPH & AD

Zilkha Neurogenetic Institute B Zlokovic Nature Neuroscience Dec 2011

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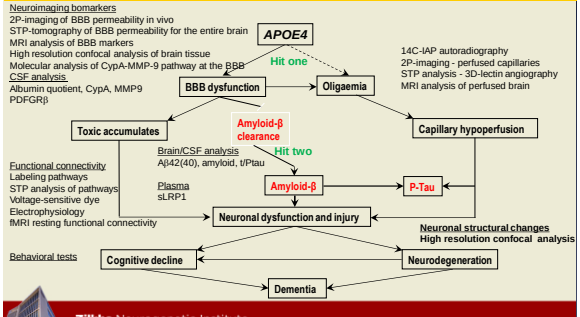
TESTING TWO-HIT VASCULAR HYPOTHESIS IN ANIMAL MODELS ON DIFFERENT *APOE* GENOTYPE

***TRE* knock-in mice**
**3 x Tg mice**




Zilkha Neurogenetic Institute

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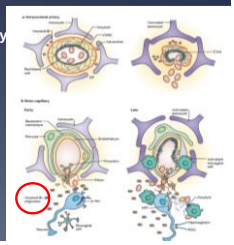
## ApoE Aβ-independent functions

**HUMAN DATA**

- ***APOE4* carriers: reductions in neurovascular functions (e.g., flow, glucose transport)**
- **AD - BBB breakdown more common in individuals with at least one *APOE4* allele**
- **AD - collapsed vessels, reduced capillary density**

**MOUSE DATA**

- ***Apoe*$^{-/-}$: BBB breakdown**
- ***APOE4* - BBB susceptibility to injurious stimuli**



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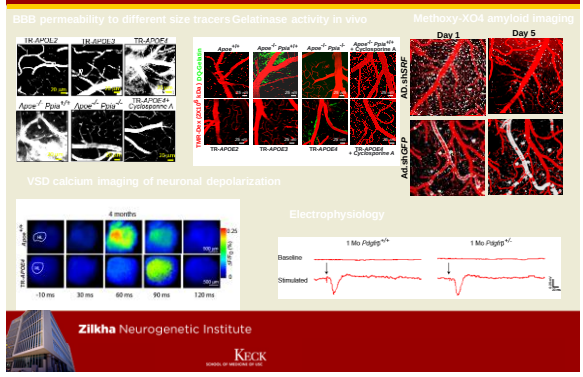
Imaging in vivo techniques in mice
2P-imaging, VSD, electrophysiology

Bell...Zlokovic, Nature 2012
Bell, Winkler....Zlokovic, Neuron, 2010
Bell....Zlokovic, Nature Cell Biology, 2009

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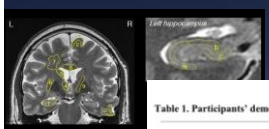
Keck School of Medicine of USC

## BBB breakdown in the hippocampus in the living human brain during normal aging (Neuron 2015)



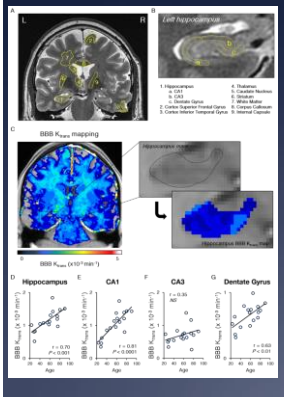
**BBB changes with age**
**BBB changes with memory impairment**
**BBB and APOE4**
**BBB albumin and pericyte dysfunction**

**Table 1. Participants' demographic information.**

| | NCI, young | NCI, older | MCI | MS |
|---|---|---|---|---|
| Clinical Dementia Rating scale | 0 | 0 | 0.5 | 0 |
| Number of participants | 16 | 18 | 21 | 19 |
| Female, % | 56.3 | 55.6 | 52.4 | 63.2 |
| Age range | 23-47 | 55-91 | 55-85 | 26-53 |
| DCE-MRI | 16/16 | 18/18 | 20/21 | 19/19 |
| Lumbar puncture | 0/16 | 15/18 | 17/21 | 0/19 |
| Age at lumbar puncture, Mean (SD) | N/A | 73.2 (10.6) | 72.0 (8.5) | N/A |

*NCI, no cognitive impairment; MCI, mild cognitive impairment; MS, multiple sclerosis; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; SD, standard deviation; N/A, not applicable.*

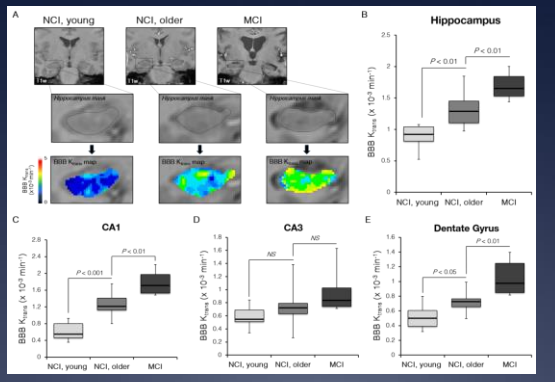
Axel Montagne[1], Samuel R. Barnes[2], Melanie D. Sweeney[1], Matthew R. Halliday[1], Abhay P. Sagare[1], Zhen Zhao[1], Arthur W. Toga[3], Russell E. Jacobs[2], Collins Y. Liu[4,5], Helena C. Chui[4], Meng Law[5], Berislav V. Zlokovic[1*].



## BBB breakdown in the hippocampus in the living human brain during normal aging (Neuron 2015)

Age-dependent increase in the BBB permeability $K_{trans}$ constant in the entire hippocampus, its CA1 region and dentate gyrus, but not CA3 region. Single data points for the $K_{trans}$ constant from 17 individuals with no cognitive impairment

Axel Montagne[1], Samuel R. Barnes[2], Melanie D. Sweeney[1], Matthew R. Halliday[1], Abhay P. Sagare[1], Zhen Zhao[1], Arthur W. Toga[3], Russell E. Jacobs[2], Collins Y. Liu[4,5], Helena C. Chui[4], Meng Law[5], Berislav V. Zlokovic[1*].




Axel Montagne, Meng Law, Berislav V. Zlokovic et al. Neuron Jan 2015.

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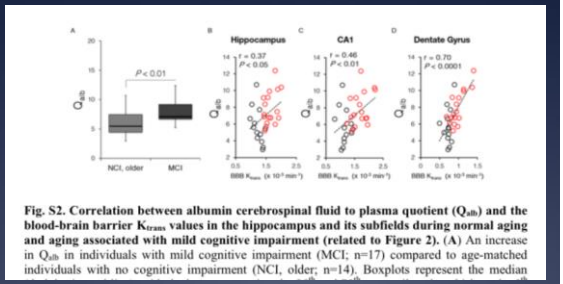
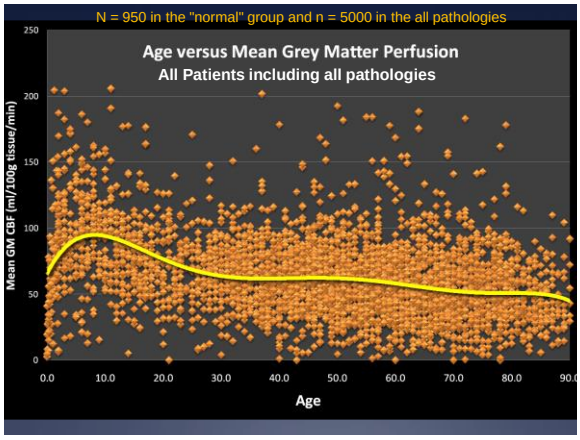


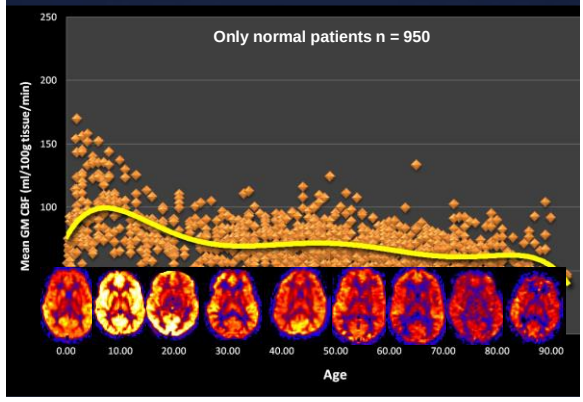

**Fig. S2. Correlation between albumin cerebrospinal fluid to plasma quotient ($Q_{alb}$) and the blood-brain barrier $K_{trans}$ values in the hippocampus and its subfields during normal aging and aging associated with mild cognitive impairment (related to Figure 2).** (**A**) An increase in $Q_{alb}$ in individuals with mild cognitive impairment (MCI; n=17) compared to age-matched individuals with no cognitive impairment (NCI, older; n=14). Boxplots represent the median

Axel Montagne[1], Samuel R. Barnes[2], Melanie D. Sweeney[1], Matthew R. Halliday[1], Abhay P. Sagare[1], Zhen Zhao[1], Arthur W. Toga[3], Russell E. Jacobs[2], Collins Y. Liu[4,5], Helena C. Chui[4], Meng Law[5], Berislav V. Zlokovic[1*].

N = 950 in the "normal" group and n = 5000 in the all pathologies

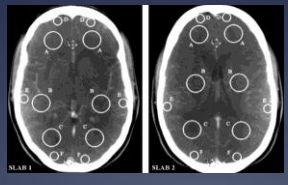



## Age vs. Mean Perfusion



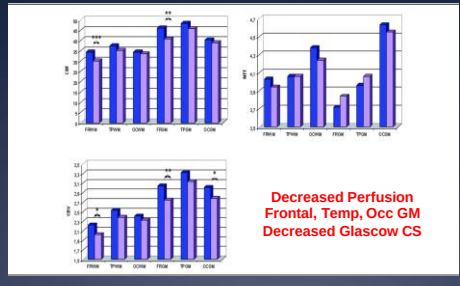

## Brain Trauma CT perfusion

- Seventy-six patients were included. In patients with a decreased Glasgow Coma Scale score
- In the acute phase of mild head injury, disturbed cerebral perfusion is seen in patients with normal noncontrast CT correlating with severity of injury and outcome



Metting Z et al. Perfusion computed tomography in the acute phase of mild head injury: Regional dysfunction and prognostic value, Annals of Neurology June 2009 Pages 809 - 816

## Brain Trauma CT perfusion



**Decreased Perfusion**
**Frontal, Temp, Occ GM**
**Decreased Glascow CS**

Metting Z et al. Perfusion computed tomography in the acute phase of mild head injury: Regional dysfunction and prognostic value, Annals of Neurology June 2009 Pages 809 - 816

## Exercise Plays a Preventive Role Against AD?

- Yaffe K, Barnes D, Nevitt M, et al. A prospective study of physical activity and cognitive decline in elderly women who walk. Arch Intern Med 2001
- Lytle ME, Vander Bilt J, Pandav RS, et al. Exercise level and cognitive decline. The MoVIES Project. Alzheimer Dis Assoc Disord 2004
- Van Gelder BM, Tijhuis MAR, Kalmijn S, et al. Physical activity in relation to cognitive decline in elderly men. The FINE Study. Neurology 2004
- Weuve J, Hee Kang J, Manson JE, et al. Physical activity, including walking, and cognitive function in older women. JAMA 2004; 292:1454–1561. This is the largest observational study to date. It confirmed the association between physical activity and cognitive decline.
- Verghese J, Lipton RB, Kartz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003

Radak et al. JAD Volume 20, Number 1 / 2010

## Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial

- OBJECTIVE: To determine whether physical activity reduces the rate of cognitive decline among older adults at risk
- CONCLUSIONS: In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period

Lautenschlager NT JAMA. 2009 Jan 21;301(3):276

Extended Practice and Aerobic Exercise Interventions Benefit Untrained Cognitive Outcomes in Older Adults: A Meta-Analysis

*Shoshana B. Hindin, BS, and Elizabeth M. Zelinski, PhD*

**OBJECTIVES:** To examine whether therapeutic interventions of extended practice of cognitive tasks or aerobic exercise have led to significant improvement in untrained cognitive tasks.

**DESIGN:** The PSYCINFO, MEDLINE, and Abstracts in Social Gerontology databases were searched for English-language studies of cognitive interventions of exercise or extended cognitive practice between 1966 and 2010. The final search was in January 2011. Studies included were experimental interventions hypothesizing improvement on untrained cognitive outcomes with pre- and posttests. Studies of varying quality were included and compared.

**SETTING:** Interventions generally took place in laboratories, in gymnasium facilities, in the home, and outdoors. Experimenters administered testing.

**PARTICIPANTS:** Forty-two studies with 3,781 healthy older adults aged 55 and older were analyzed.

**MEASUREMENTS:** Between-group effect sizes (ESs), which account for practice effects on outcome measures, and within-experimental group ESs were computed from untrained cognitive outcome domains, including choice reaction time, memory, and executive function, and compared. ESs were also coded for training type and study quality. Multilevel mixed-effect analyses accommodated multiple outcomes from individual studies.

**RESULTS:** Extended practice (estimated ES = 0.33, 95% confidence interval (CI) = 0.13–0.52) and aerobic fitness (estimated ES = 0.33, 95% CI = 0.10–0.55) training produced significant between-group ESs, but they did not differ in magnitude. Better study quality was associated with larger ESs.

**CONCLUSION:** Findings indicate that aerobic and extended cognitive practice training interventions for healthy older adults improve performance on untrained cognitive tasks. **J Am Geriatr Soc 60:136–141, 2012.**

From the Davis School of Gerontology, University of Southern California, Los Angeles, California.

**Key words:** cognitive intervention; cognitive training; meta-analysis; aerobic exercise; cognitive decline

The National Institutes of Health recently published a State of the Science Conference statement on preventing Alzheimer's disease and cognitive decline[1] that indicated that the evidence is inadequate to support a conclusion that any interventions are adequate to prevent or delay Alzheimer's disease. The conference review focused on randomized controlled clinical trials with more than 200 participants, although it suggested that there are encouraging associations of positive effects of interventions that maintain or improve cognitive function in healthy older adults, including cognitive engagement and aerobic exercise.

Both types of interventions are at an early evaluation phase for clinical practice adoption. Many studies are in Phase I or II, during which hypothesized effects of the intervention and treatment protocol are developed (Phase I) or initial exploratory studies are conducted (Phase II). A few randomized controlled trials are in Phase III. In contrast, the State of the Science review was of Phase IV and V interventions: efficacy studies to extend established positive outcomes to specified populations (Phase IV) and focusing on cost-effectiveness and intervention efficiency (Phase V).[2]

The cognitive training industry grossed an estimated $295 million in 2009.[3] It is therefore important to evaluate early-phase results of interventions for older adults. The assumption behind cognitive training is that the benefits will extend to untrained outcomes,[4] but several meta-analyses[5,6] have found only small effects of untrained test improvement.

Rita and Edward Polusky Chair in Education and Aging
Professor of Gerontology and Psychology USC

## Importance of sleep

- CSF flow approximately doubles during sleep.

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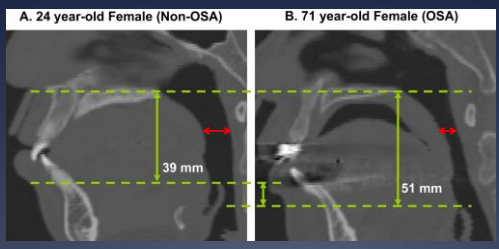
DOI: 10.1089/rej.2013.1530

**Commentaries**

Sleep Facilitates Clearance of Metabolites from the Brain: Glymphatic Function in Aging and Neurodegenerative Diseases

Andrew R. Mendelsohn and James W. Larrick

## 24yo non-OSA woman compared with a 71yo woman with *OSA*, obstructive sleep apnea




Shigeta Y, Ogawa T, Venturin J, Nguyen M, Clark GT, Enciso R 2008 Oct;106(4):563-70.

## Sleep Apnea and AD

Obstructive sleep apnea and cognitive impairment in the elderly
Onen F, Onen H.Psychol Neuropsychiatr Vieil. 2010 Sep;8(3):163-9. Review.

Sleep apnea, APE-4 and TBI: mechanism for cognitive dysfunction and develeopment of dementia. O'Hara R, Luzon A, Hubbard J, Zeitzer JM.J Rehabil Res Dev. 2009;46(6):837-50. Review

Sustained use of CPAP slows deterioration of cognition, sleep and mood in AD and obstructive sleep apnea. Cooke JR, Ayalon L, Palmer BW, Loredo JS, Corey-Bloom J, Natarajan L, Liu L, Ancoli-Israel S.J Clin **Sleep** Med. 2009 Aug 15;5(4):305-9.

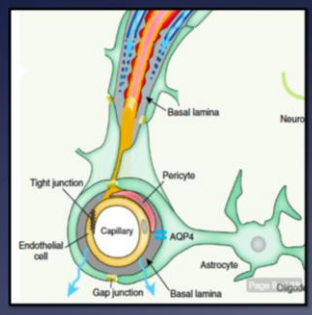
Sleep apnea in AD: Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, Liu L, Ayalon L, He F, Loredo JS.J Am Geriatr Soc. 2008 Nov;56(11):2076-81. Epub 2008 Sep 15.

Add Alzheimner's Disease to the list of sleep apnea consequences. Abrams B. Med Hypotheses. 2005;65(6):1201-2. Epub 2005 Aug 8

## Glymphatic system

- Highly polarized macroscopic system of fluid fluxes with rapid, continuous interchange of CSF and interstitial fluid (ISF)
- Facilitated by convective influx of CSF along periarterial space
- CSF driven into VRS by:
  - Arterial pulsatility
  - Respiration
  - Slow vasomotion
  - CSF pressure gradients
- CSF movement into parenchyma facilitated by AQP4 channels
- This CSF movement drives convective interstitial fluid fluxes within the parenchyma then toward perivenous spaces
- Subsequently drains toward cervical lymphatic system

## Glymphatic system

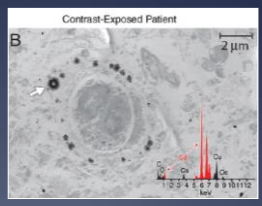



- CSF – ISF exchange occurs at astrocyte endfeet (complete coverage over brain microvasculature)
- Solutes that lack specific molecular transport pathway (such as ion transporters or channels) must pass through the 20 nm cleft between overlapping endfoot process to access the interstitial space
- In a rat model, Iliff et al. found that larger MW GD tracers remain largely confined to paravascular space

## Human GD Deposition in Perivascular Spaces

- X-ray microanalysis revealed gadolinium predominently in large foci within the endothelial wall
- 18-42% had crossed the blood-brain barrier and was deposited into the neural tissue interstitium

TEM micrograph and X-ray spectrum showing the presence of gadolinium in electron-dense foci in a gadodiamide-exposed patient




31 McDonald RJ. et al., Radiology, 2015;275:772-782

## Glymphatic dysfunction: Aging

- In aged mice, 80-90% reduction in glymphatic function
- Depolarization correlates with CSF-ISF exchange, suggesting glymphatic dysfunction partly due to dysregulation of astroglial water transport
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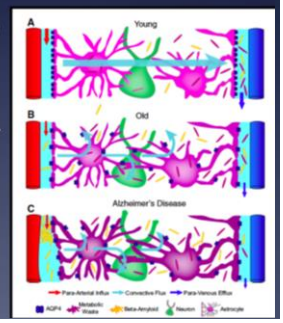
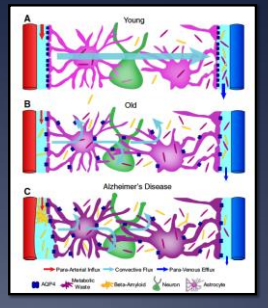



## Glymphatic dysfunction: AD

### Is this related to decreased perfusion?

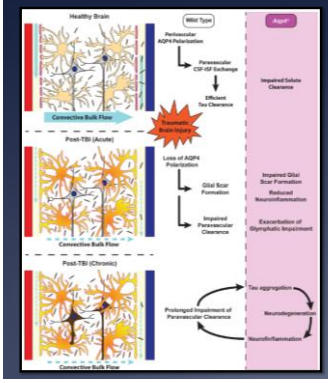
- Dysfunction of this clearance system likely important in many neurodegenerative diseases (accumulation of proteins)
- AD characterized by accumulation of proteins (amyloid, tau)
  - Iliff et al found that beta-amyloid is cleared by glymphatic system along paravenous pathway
    - Injection of fluorescent or radiolabeled amyloid beta into mouse striatum
    - AQP4 knockout mice 65% reduction in CSF fluid flux through parenchyma
    - 55% reduced clearance of labeled beta amyloid
- Beta amyloid accumulation in PVS of penetrating arteries




## Glymphatic system dysfunction:TBI

- TBI induces accumulation of beta amyloid peptide and C tau
  - C-tau correlates with severity of TBI: biomarker
  - Hypothesized that increased interstitial tau may lead to cellular uptake and fibrillary aggregation
- Formation of large astroglial scars and persistent activation of innate inflammation
  - Loss of polarization (AQP4 from feet to parenchymal processes-like aging)
- Iliff et al showed that tau accumulates around large veins and amount remaining in tissue correlates with decrease in glymphatic clearance → suggests glymphatic removal of tau important in limiting secondary neuronal damage following TBI

## Glymphatic dysfunction: TBI &



**Post traumatic impairment of the glymphatic pathway promotes tau aggregation**

**Loss of perivascular AQP4 polarization after TBI impairs paravascular clearance of interstitial solutes including tau**

**Promotes accumulation of phosphorylated tau → neurodegeneration, persistent inflammation → cognitive dysfunction**

**A mechanism for degeneration of aging neuronal membranes that leads to abnormal amyloid precursor protein processing and Alzheimer's disease**

**Investigator:** Michael G. Harrington, MB, ChB, FRCP, Program Director, Molecular Neurology Department, HMRI, 99 N. El Molino Avenue, Pasadena, CA, 91101. mghworks@hmri.org, (626) 795-4343 ext 218
**Co-Investigators:** A.N. Fonteh (HMRI), Katie Castor (HMRI), Helena Chui, Carol Miller.

**ADRC sponsor:** Helena Chui

Brain-derived membrane nanoparticles in cerebrospinal fluid (CSF)[1] have oxidized lipids in AD[2] and as early as preclinical AD[3]. To further test this hypothesis, we propose to compare membrane morphology and biochemistry in CSF and brain subcellular fractions from USC ADRC to test if CSF findings replicate in brain. Success of this project should enable a strong independent NIH funding proposal.

**Specific Aims**

1) Measure fatty acid, sphingolipid, phospholipid, APP and β-amyloid concentrations in nanoparticles from CSF, and in plasma membrane/mitochondria/synaptic vesicle preparations from the same cognitively healthy control (n = 5) and AD (n = 5) brains.
2) Measure the thicknesses in CSF nanoparticles and brain subcellular membranes.
3) Determine whether the changes in Aims 1 & 2 are a) similar in brain and CSF; b) support an early mechanism for APP distribution and the redox post-mitotic hypothesis.

## Shunting for dementia?

**Assessment of low-flow CSF drainage as a treatment for AD**

**Results of a randomized pilot study**

G.D. Silverberg, MD; E. Levinthal, PhD; E.V. Sullivan, PhD; D.A. Bloch, PhD; S.D. Chang, MD; J. Leverenz, MD; S. Flitman, MD; R. Winn, MD; F. Marciano, MD; T. Saul; S. Huhn, MD; M. Mayo, Pharm D; and D. McGuire, MD

**Abstract**—*Objective:* This prospective, randomized, controlled study was designed to investigate the safety, feasibility, and preliminary efficacy of long-term CSF drainage via a low-flow ventriculoperitoneal shunt in subjects suffering from AD. *Methods:* Twenty-nine subjects selected for probable AD (National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Dementias Association criteria) were screened to exclude normal pressure hydrocephalus or other etiologies of dementia and randomized to treatment (shunt) or no treatment groups. The study endpoint was the comparison of group performance on psychometric testing at quarterly intervals for 1 year. Shunted subjects had CSF withdrawn for MAP-tau and $A\beta_{1\text{-}42}$ assays at the same time intervals. *Results:* There was no mortality from the surgical procedure, and no patient sustained a subdural hematoma. Five notable postoperative adverse events, which resolved without permanent neurologic deficit, were reported in the shunt group. Group mean Mattis Dementia Rating Scale total scores showed little change over the year in the shunt-treatment group, in contrast to a decline in the control group ($p = 0.06$). Mini-Mental State Examination mean scores supported a trend in favor of shunt treatment ($p = 0.1$). There was a concomitant decrease in ventricular CSF concentrations of AD biomarkers MAP-tau and $A\beta_{1\text{-}42}$. *Conclusions:* The surgical procedure and the device are reasonably safe. Adverse events were consistent with shunt procedures for hydrocephalus in this older population. The endpoint data show a trend in favor of the treated group. A larger, randomized, double-blinded, controlled, clinical trial is underway.

NEUROLOGY 2002;59:1139–1145

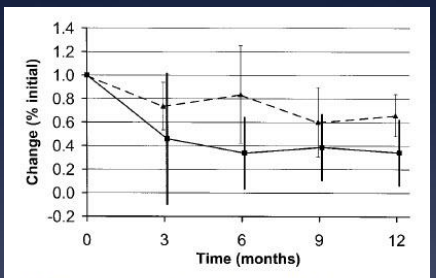



*Figure 3. Percentage change from baseline in ventricular CSF concentrations of $A\beta_{(1\text{-}42)}$ and MAP-tau over the 12-month study period. Triangles represent $A\beta_{(1\text{-}42)}$ and squares represent MAP-tau.*

## Glymphatic dysfunction:Stroke

Gaberel et al (Stroke 2014) suggest glymphatic system impaired after acute embolic stroke, SAH

Glymphatic function restored after spontaneous arterial recanalization

Ventricular injection of tPA improved glymphatic perfusion after SAH

Glymphatic dysfunction after acute stroke may prevent adequate clearance of excitatory neurotransmitters and promote neuronal death

This potentially reversible dysfunction may result from: decrease in arterial pulsation because of vessel occlusion or occlusion of perivascular space by extrinsic compression

## Abnormal CSF flow

- Implicated in the etiology of Normal pressure hydrocephalus, Vascular dementia, Alzheimer's disease, intracranial hypertension
- Vascular disease (one potential cause of abnormal CSF flow) results in a decrease in cerebral arterial compliance
- Hydrocephalus (another cause) results is abnormal pressure gradients and changes brain compliance

## NPH

- Loss of brain elasticity results in arterial pressure transmitted to the incompressible CSF in ventricles
- Imaging findings:
  - Ventriculomegaly out of proportion to subarachnoid space
  - Prominent periventricular halo
  - Hyperdynamic flow through aqueduct
    - CSF flow void in the cerebral aqueduct
    - Elevated velocity on Phase contrast MRI

## Abnormal CSF flow

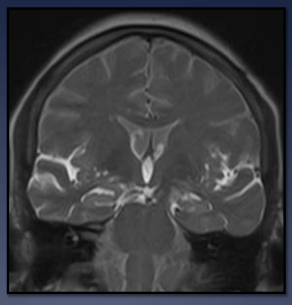
- Implicated in the etiology of vascular dementia, Alzheimer's disease, late-onset depression, intracranial hypertension, NPH, leukoaraiosis.
- Vascular disease (one potential cause of abnormal CSF flow) results in a decrease in cerebral arterial compliance.
- Hydrocephalus (another cause) results is abnormal pressure gradients and perhaps changes brain compliance.
- Metabolic Waste Clearance
- Peripheral Immune Surveillance
- Cell trafficking Pathway
- Route for Signaling Molecule Distribution

Role of CSF

## Time-SLIP Technique

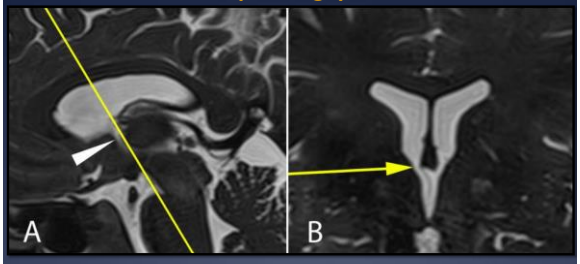
15 different TI values at 200msec intervals starting at 2000msec

Total acquisition time = 3.5 minutes depending on the pulse rate

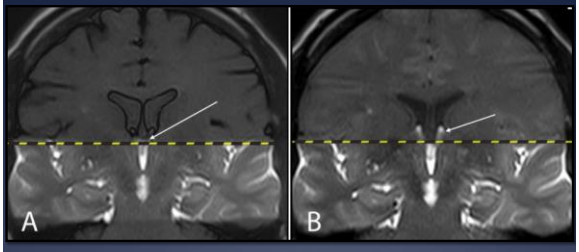


Normal reflux from 3rd to lateral ventricles

## Scan setup: Tag placement

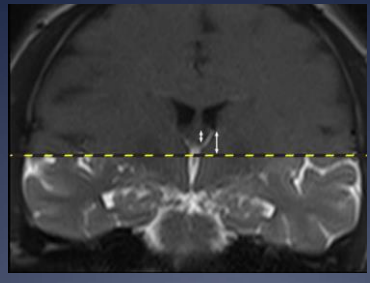



## Tag placement

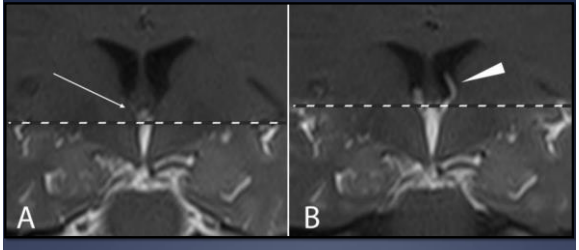



The top of the tag is placed at the inferior margin of the septum pellucidum

Measurements from the upper margin of the tag vs. inferior margin of septum pellucidum to the upper point of reflux



## Tag placement matters

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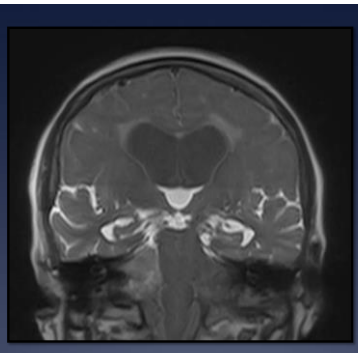
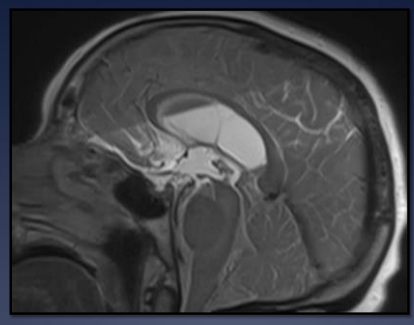
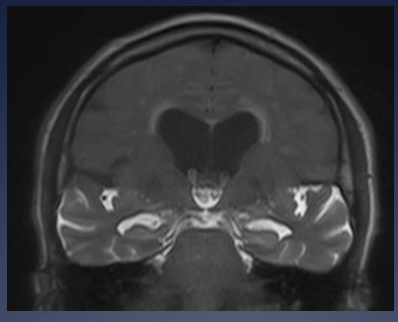
    - Hyperdynamic flow



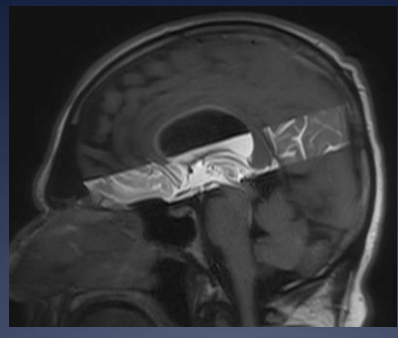
Patient 1 with NPH Responded to shunting



Patient 1 with NPH Responded to TV/shunting



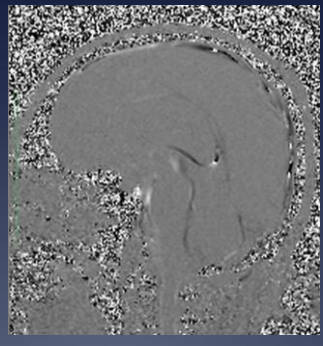
Patient 2 with NPH Responded to shunting



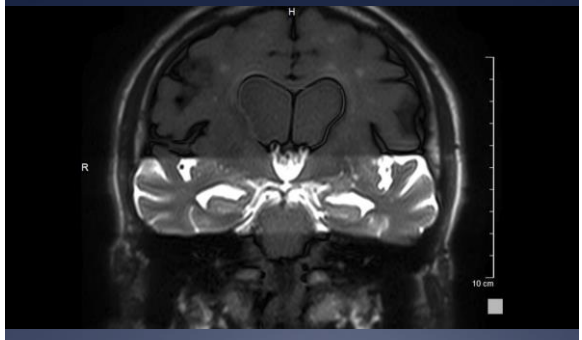
Patient 2 with NPH Responded to shunting

Patient 2 with NPH Responded to shunting

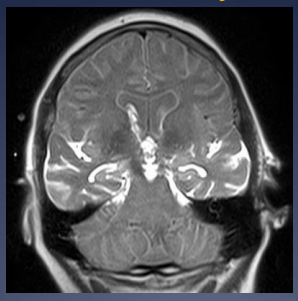
Aliasing artifact at the cerebral aqueduct because the venc is set too low



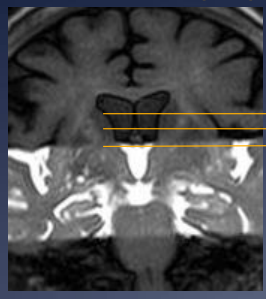
## Parkinson's Disease



## Reflux of CSF into Lateral Ventricles in patients with memory complaints

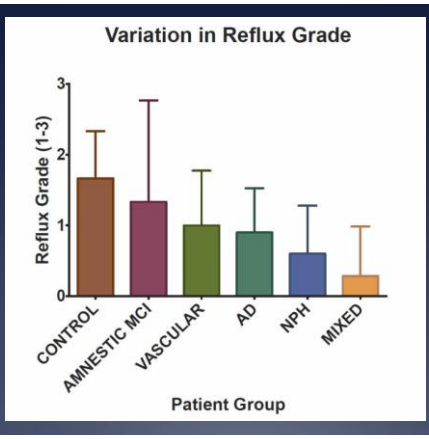


## Study to evaluate CSF reflux with dementia (51 patients so far)




Grading the amount of reflux

Jeffrey A. Bennett, MD University of Florida





*4D CSF Time-SLIP: intra-ventricular CSF*

## Marker of brain compliance Perfusion, CSF flow, BBB

- Many degenerative diseases involve an inflammatory & vascular component along with changes in brain compliance.
- Altered CSF flow reducing the clearance of toxic proteins such as beta amyloid.
- Effect of CSF flow, glymphatic drainage
- Related to perfusion and venous clearance

## 10 Strategies (some surprises)

- 1. Coffee: caffeine, anti-oxidant effects, stimulant
- 2. Floss & periodontal disease, inflammation
- 3. Googling and Internet searching
- 4. Aerobic exercise 30 mins a day
- 5. Apple a day or apple juice – acetylcholine
- 6. Prevent head blows
- 7. Meditation & Sleep: improved blood flow/glymplatics
- 8. Vitamins, esp Vitamin D, Menopause & HRT?
- 9. Mental Stimulation: play music instrument, language
- 10. Avoid Infections cold sores, gastric ulcers, Lyme disease, pneumonia and the flu

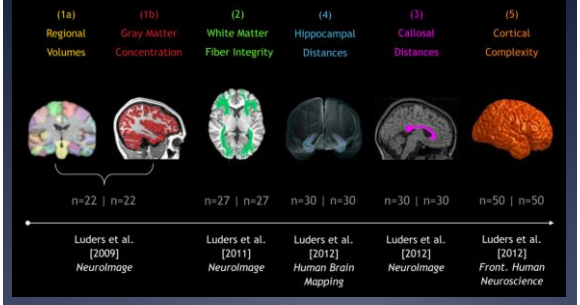
Jean Carper's newest book: "100 Simple Things You Can Do to Prevent Alzheimer's"

Keck School of Medicine
Viterbi Engineering School

# Summary

- Hypothesis: BBB, Brain Perfusion, Glymphatics & Brain Compliance
  - Everything gets smaller or less as you get older: Bill Bradley
- Abnormal BBB DCE MRI in MCI and AD
  - Correlation with CSF markers and CSF flow (Zlokovic, Law, Chui et al)
- What is Normal flow of CSF and ISF?
  - Diffusion Flow
  - Arterial Pulsatility, CSF – ISF Gradients
  - Drainage of CSF – Relative contributions unknown from
    - Arachnoid granulations
    - Perineural nerve sheaths
    - Drainage into the dural lymphatics/glymphatics then neck
- Cine Phase Contrast & Time Slip Spin Imaging of CSF Flow

# Effect of Mindfulness and Neural Plasticity




*Real Time Imaging*
*Auto Tracing (Dynatracer)*