GRAL, BNI, Jan 29th 2025

Is there a role of CSF-to-blood-clearance for cognitive function?

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for Brain Fluid Research

CSF clearance and cognitive function

Clinical neurosurgery: Vascular / CSF / Skull base

Research: Neurovascular – CSF Research group

Potential Conflict of Interest Disclosure

Shareholder in BrainWideSolutions AS, Oslo, Norway, which is a holder of patents US 11,272,841 and US 12,016,651.

Brain waste removal and Cognitive function

Human brain (about 1.4 kg – 2% of body weight)

- ✓ High energy demand - about ¼ of body's energy supply
- ✓ Cerebral circulation – about 1/5 of cardiac output.

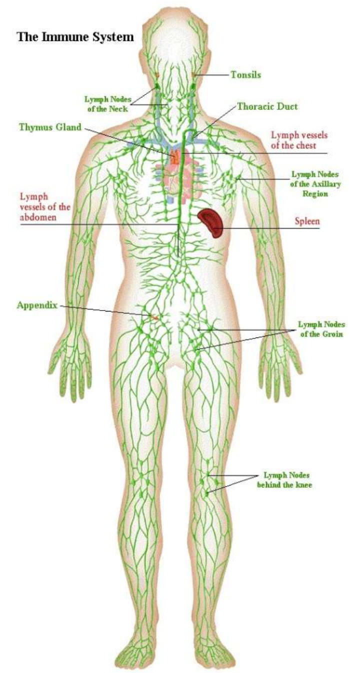
Produces about 3 to 4 grams of proteins each day
(x3-4 higher rate than skeletal muscles)

All energy-processes produce waste - some are toxic: Amyloid-β / tau / α-synuclein

Cerebral *proteinopathies*: Abnormal protein aggregation in brain

How does the brain handle its waste created by brain metabolism?

In other organs the lymphatic system crucial for:
- i) waste clearance
- ii) immunosurveillance



Main pathways in the brain:
1. Transport of solutes across blood-brain-barrier (BBB).
2. Cellular degradation (intra- and extra-cellular)
3. CSF/ISF-mediated

Role of CSF elimination rate in cognitive function / dementia

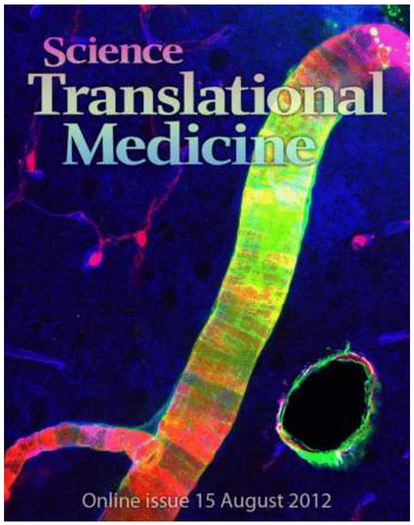
Role of CSF in transport of solutes – two recent major discoveries

2012: The glymphatic system: A brain-wide perivascular transport route for fluids and solutes

2015: The meningeal lymphatic system: Lymphatic vessels in dura mater draining CSF

Discoveries made in rodents - translation to humans?

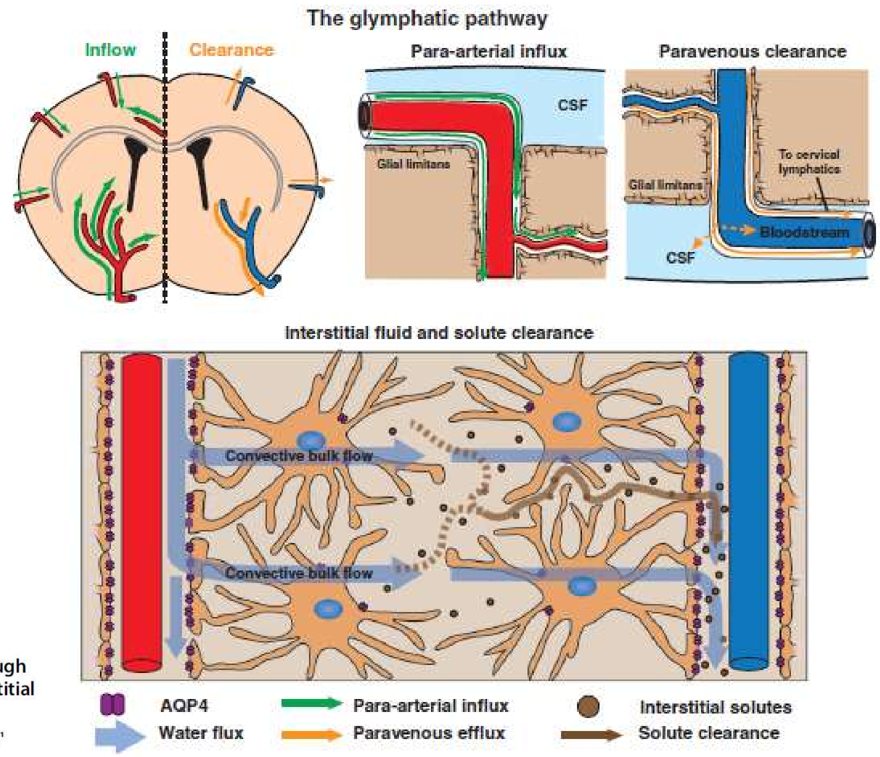
2012: The glymphatic system

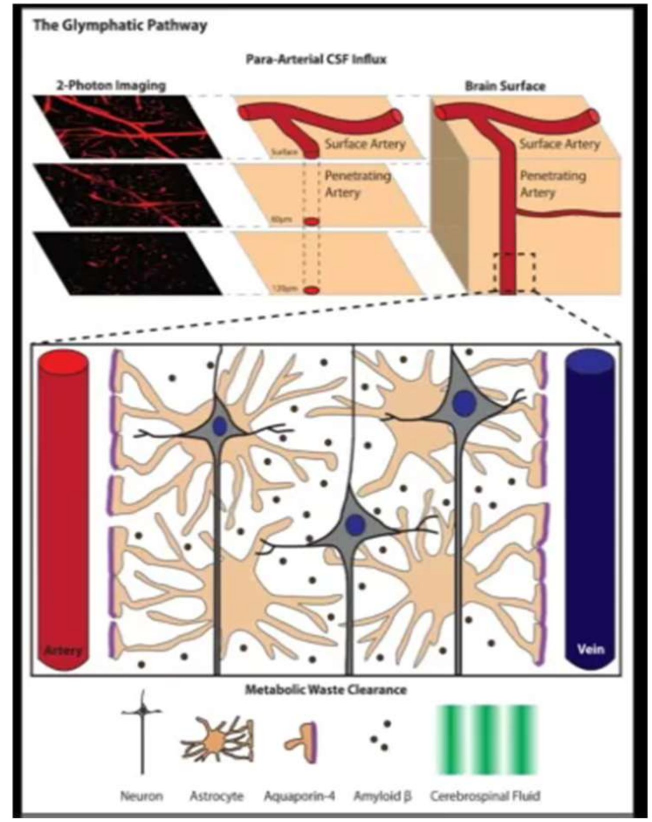


CEREBROSPINAL FLUID CIRCULATION

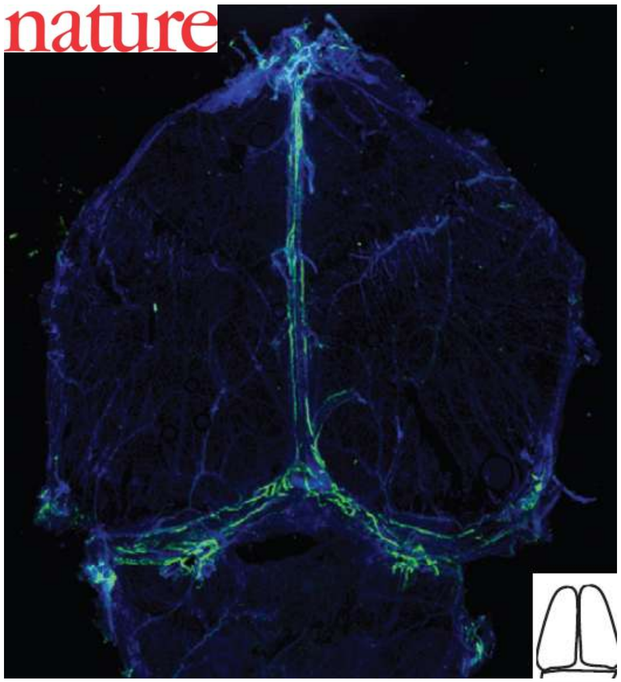
A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β

Jeffrey J. Iliff,[1]* Minghuan Wang,[1,2] Yonghong Liao,[1] Benjamin A. Plogg,[1] Weiguo Peng,[1] Georg A. Gundersen,[3,4] Helene Benveniste,[5,6] G. Edward Vates,[1] Rashid Deane,[1] Steven A. Goldman,[1,7] Erlend A. Nagelhus,[3,4] Maiken Nedergaard[1]*





2015: The meningeal lymphatic system



Structural and functional features of central nervous system lymphatic vessels

Antoine Louveau[1,2], Igor Smirnov[1,2], Timothy J. Keyes[1,2], Jacob D. Eccles[3,4,5], Sherin J. Rouhani[3,4,6], J. David Peske[3,4,6], Noel C. Derecki[1,2], David Castle[7], James W. Mandell[8], Kevin S. Lee[1,2,9], Tajie H. Harris[1,2] & Jonathan Kipnis[1,2,3]

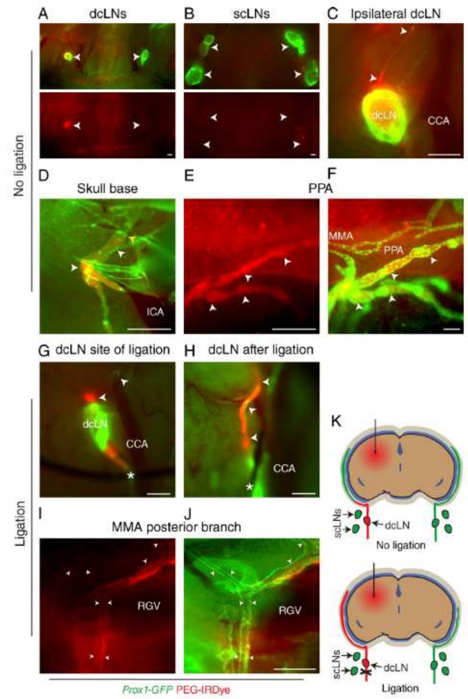


Figure 2. Dura mater lymphatic vessels drain brain ISF into dcLNs. (A–J) Analysis of lymphatic outflow routes of cerebral ISF by fluorescent stereomicroscopy in *Prox1-GFP* (green) mice 1 h after PEG-IRDye (red) injection into the brain parenchyma without (A–F) and with (G–J) ligation of the efferent lymphatic vessel of the dcLN. See K for schematic illustration of the experimental setup and summary of the results with and without ligation. (A and B) dcLNs and scLNs (both indicated with arrowheads) showing preferential filling of the ipsilateral dcLN but no filling in the scLNs. (C) Drainage into the ipsilateral dcLN via the efferent carotid lymphatic vessels (arrowheads). CCA, common carotid artery. (D) Internal carotid artery (ICA) and adjacent lymphatic vessels (white arrowheads) immediately below the osseous skull, showing drainage from the skull (yellow arrowhead). (E and F) Lymphatic vessels around the pterygopalatine artery (PPA), showing tracer uptake by the dura mater lymphatic vessels (arrowheads) only in the basal parts of the skull, nearby their exit site. MMA, middle meningeal artery. (G) Placement of a suture around the efferent lymphatic vessel (asterisk) of the dcLN. Arrowheads, afferent lymphatic vessels. (H) Afferent lymphatic vessel of the dcLN after ligation (asterisk), showing bulging of the afferent vessels (arrowheads). (I and J) Lymphatic vessels around the posterior branch of the MMA, showing increased filling of lymphatic vessels after ligation, extending above the retroglenoid vein (RGV) level. $n = 2–3$/group. Data are representative of two independent experiments. Bars: (A–E and G–J) 500 µm; (F) 100 µm.

Published June 15, 2015
JEM Brief Definitive Report

A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules

Aleksanteri Aspelund,[1,2] Salli Antila,[1,2] Steven T. Proulx,[3] Tine Veronica Karlsen,[4] Sinem Karaman,[3] Michael Detmar,[3] Helge Wiig,[4] and Kari Alitalo[1,2]

[1]Wihuri Research Institute and [2]Translational Cancer Biology Program, Biomedicum Helsinki, University of Helsinki, 00014 Helsinki, Finland
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[4]Department of Biomedicine, University of Bergen, 5009 Bergen, Norway

Glymphatic-meningeal-lymphatic transport

Larger solutes – not water per se

CSF: 99% water + 1% other substances / solutes

Outline

Studying solute transport in brain, subarachnoid space and across dura utilizing a CSF tracer

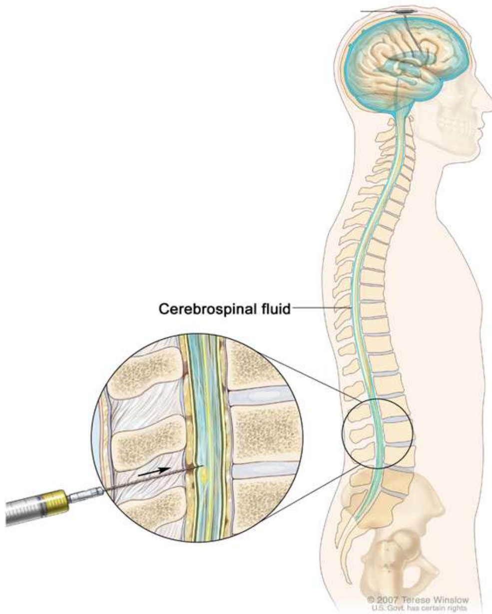
Imaging contrast agents

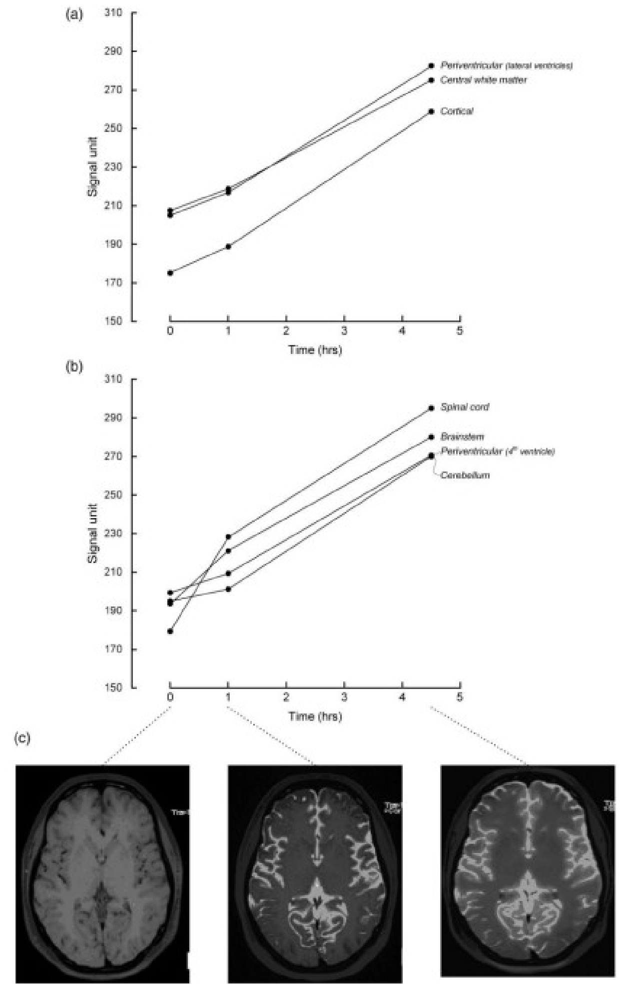
Gadobutrol: 604 Da
Iodixanol 1 550 Da

Amyloid-β – molecular weight 5.3 kDa

Tau – molecular weight 55-62 kDa

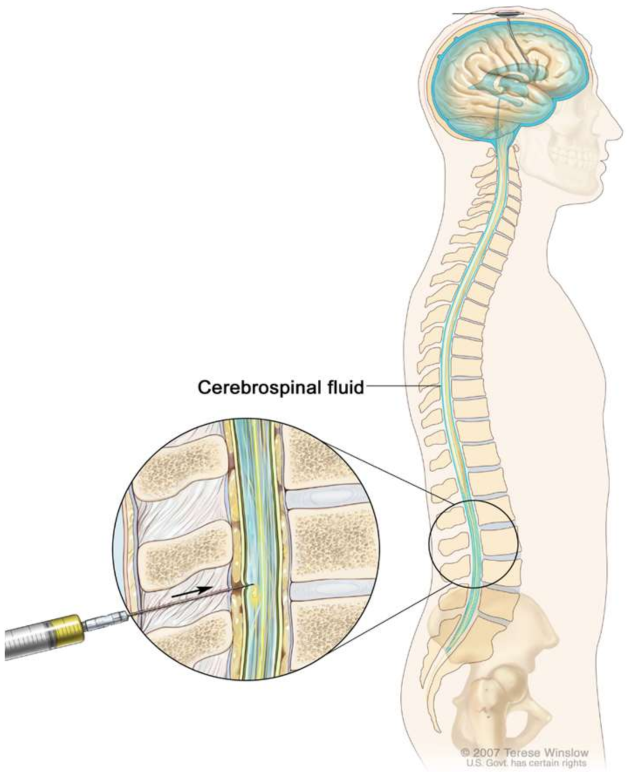
Diagnostics of CSF leakage in our institution: Intrathecal contrast-enhanced MRI

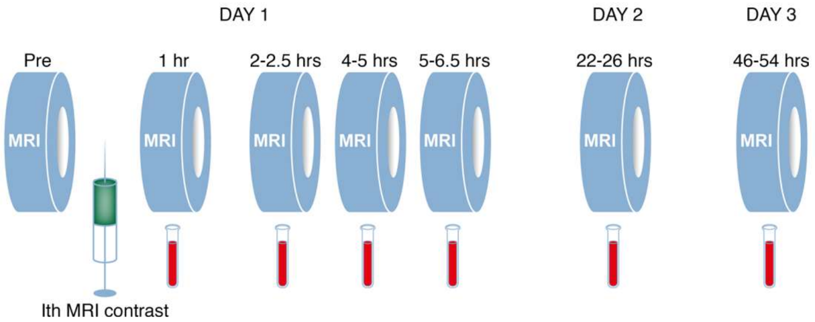




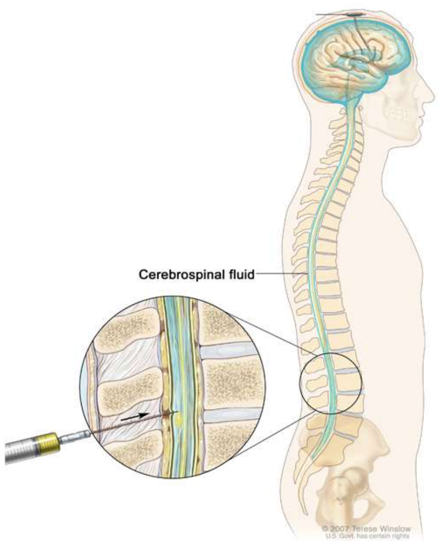
Eide & Ringstad, Acta Radiologica Open, 2015

Solute transport in human brain, subarachnoid space and beyond



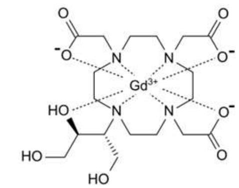


CSF tracers visualized by imaging or measured in blood



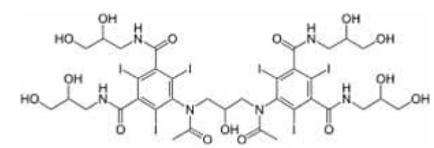
Gadobutrol (Gadovist, Bayer, GE) – off label on special permission

- Commonly used MRI contrast agent
- Hydrophilic, logP: -9.8
- Molecular weight: 604 Da, neutral compound
- Does not cross the blood-brain barrier (BBB)
- Intrathecal gadobutrol: Doses: 0.5 mmol, 0.25 mmol, 0.10 mmol
- Intrathecal use: Off-label



Iodixanol (GE HealthCare, USA) – on label

- Commonly used CT contrast agent
- Hydrophilic, logP: 0.7
- Molecular weight: 1,550 Da, neutral compound
- Intrathecal iodizanol: 270 mg/ml, 3 ml
- Intrathecal use: On label



Intratehcal gadobutrol in doses ≤ 0.50 mmol is safe

Table 1
Observed and estimated gadolinium concentrations in various body compartments after intravenous (IV) and intrathecal (IT) gadobutrol injection in clinically relevant doses (*estimated concentrations)

	IV	IT
Body dose (80 kg subject)	*8* mmol (0.1 mmol/kg)	*0.5* mmol
Blood Gd concentration (peak)	*6.0* mM[6]* (2 min, dosage 0.1 mm/kg)	*0.0014* mM[7] (~10 h)
CSF Gd concentration (peak)	*0.2* mM[8] (0.1 mmol/kg IV)	*0.5* mM[9] (0.5 mmol IT)
Brain Gd concentration (peak)	*0.04* mM[6]*	*0.1* mM[9]

ORIGINAL RESEARCH
PATIENT SAFETY

Intrathecal Use of Gadobutrol for Glymphatic MR Imaging: Prospective Safety Study of 100 Patients

C.S. Edeklev, M. Halvorsen, G. Løvland, S.A.S. Vatnehol, Ø. Gjertsen, B. Nedregaard, R. Sletteberg, G. Ringstad, and P.K. Eide

Neuroradiology
https://doi.org/10.1007/s00234-023-03198-7
DIAGNOSTIC NEURORADIOLOGY

Check for updates

Prospective T1 mapping to assess gadolinium retention in brain after intrathecal gadobutrol

Geir Ringstad[1,2] · Lars Magnus Valnes[3] · Svein Are Sirirud Vatnehol[4,5] · Are Hugo Pripp[6,7] · Per Kristian Eide[3,8]

Neuroradiology (2021) 63:51–61
https://doi.org/10.1007/s00234-020-02519-4
DIAGNOSTIC NEURORADIOLOGY

Check for updates

Off-label intrathecal use of gadobutrol: safety study and comparison of administration protocols

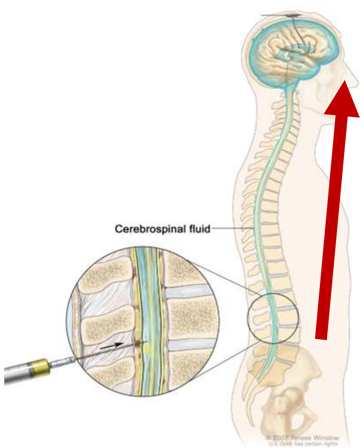
Merete Halvorsen[1] · Camilla Sæthre Edeklev[1] · Jorunn Fraser-Green[2] · Grethe Løvland[2] · Svein Are Sirirud Vatnehol[2] · Øivind Gjertsen[3] · Bård Nedregaard[3] · Ruth Sletteberg[3] · Geir Ringstad[3] · Per Kristian Eide[1,4]

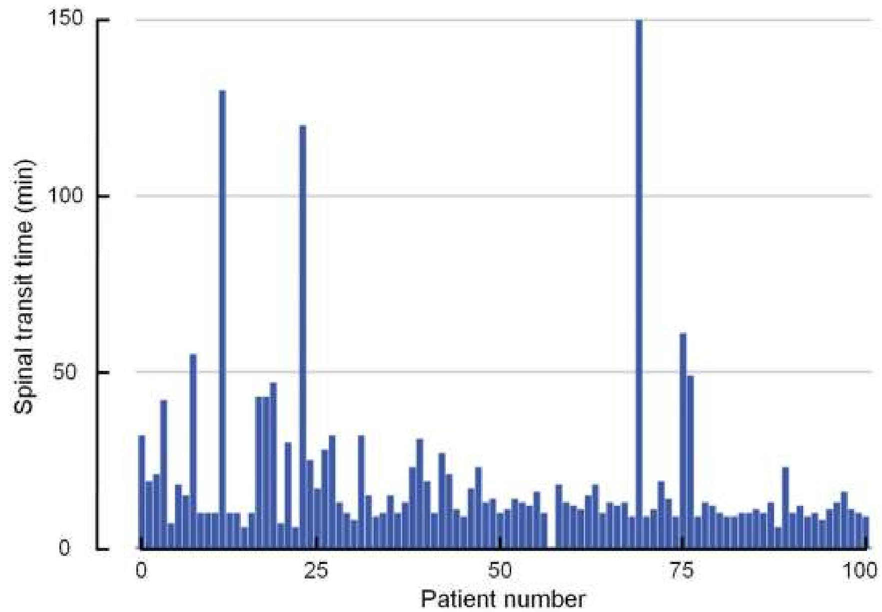
ORIGINAL RESEARCH
PATIENT SAFETY

Prospective Safety Study of Intrathecal Gadobutrol in Different Doses

A. Sperre, I. Karsrud, A.H.S. Rodum, A. Lashkarivand, L.M. Valnes, G. Ringstad, and P.K. Eide

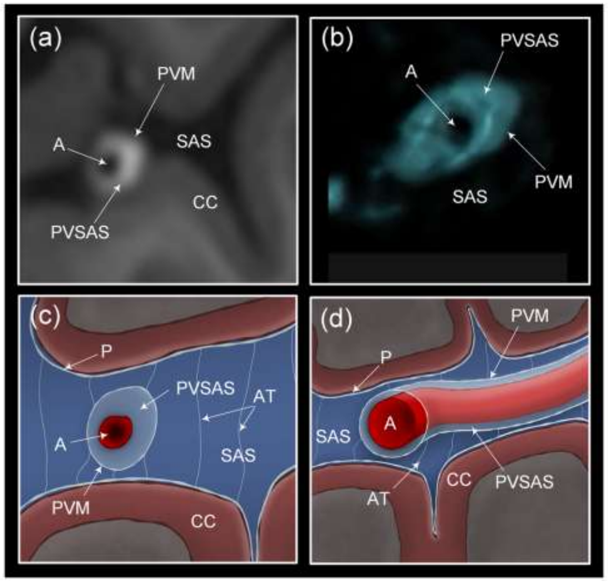
After spinal puncture at the lumbar level, the tracer typically reaches the cisterna magna after about 20 minutes, but with variation

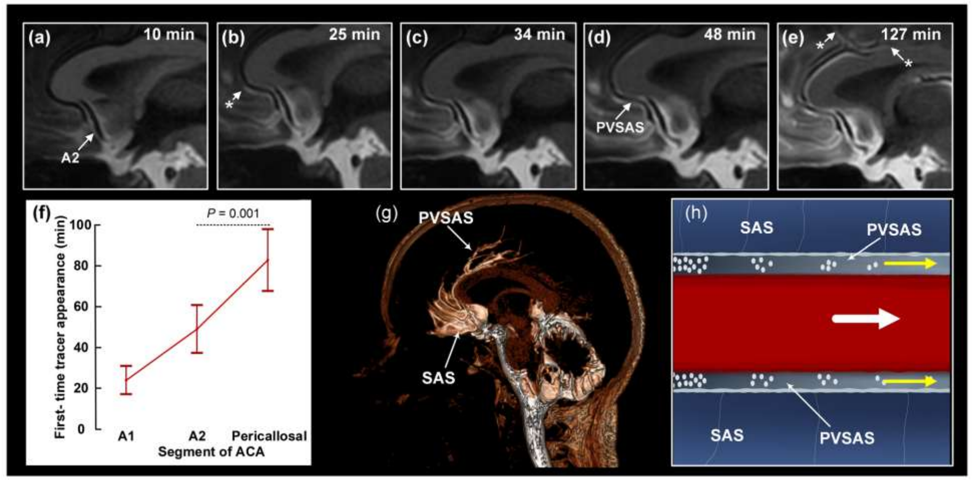


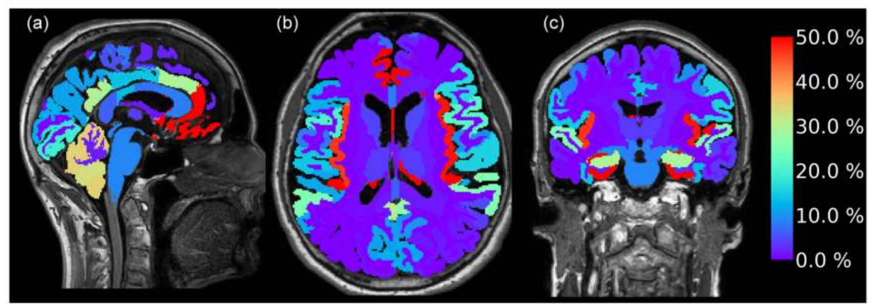


Edeklev et al., AJNR, 2019

The perivascular subarachnoid space (PVSAS) facilitates solute transport within the subarachnoid space





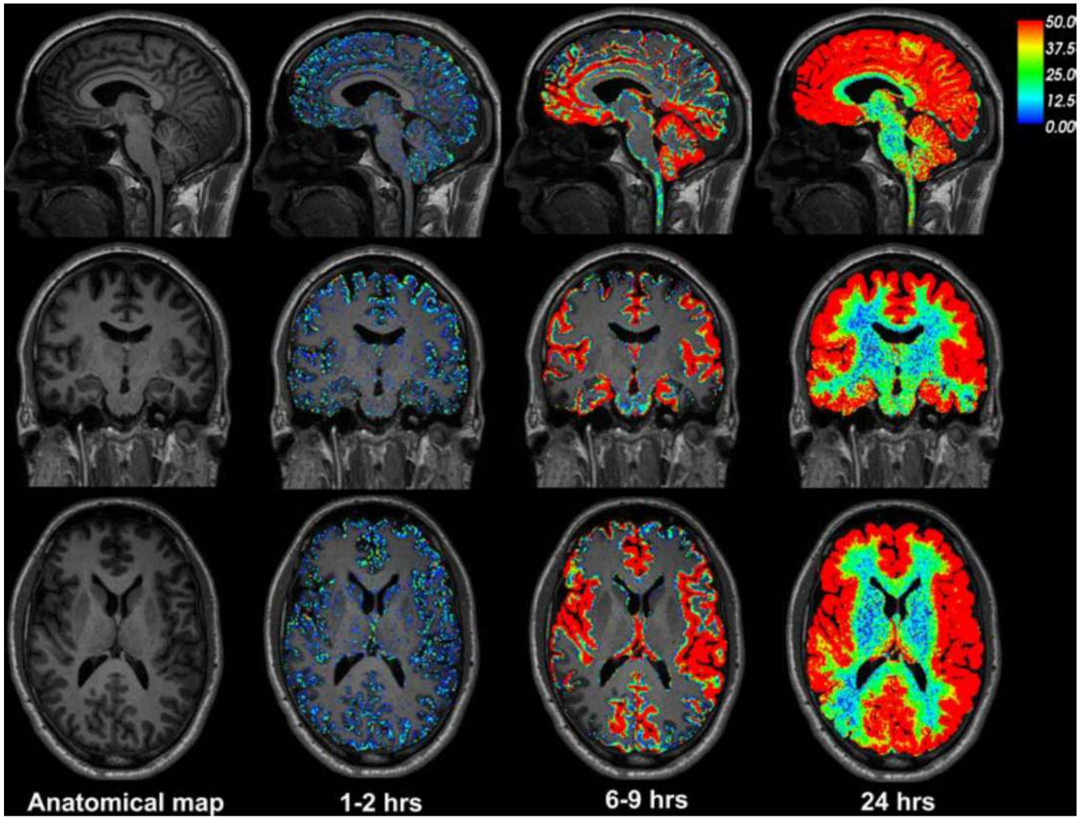


Antegrade transport along major vessels.

Degree of tracer enrichment correlates with extra-vascular brain enrichment.

Eide & Ringstad, Nature Comm, 2024

In vivo brain-wide tracer enrichment in humans



Brain-wide tracer distribution

Extra-vascular (tracer does not pass BBB)

Centripetal enrichment (from CSF and inward)

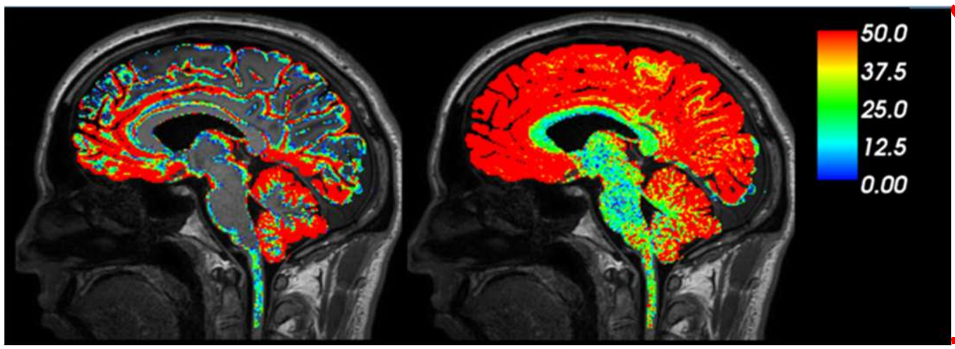
Strongest tracer enrichment in parenchyma around major arterial trunks.

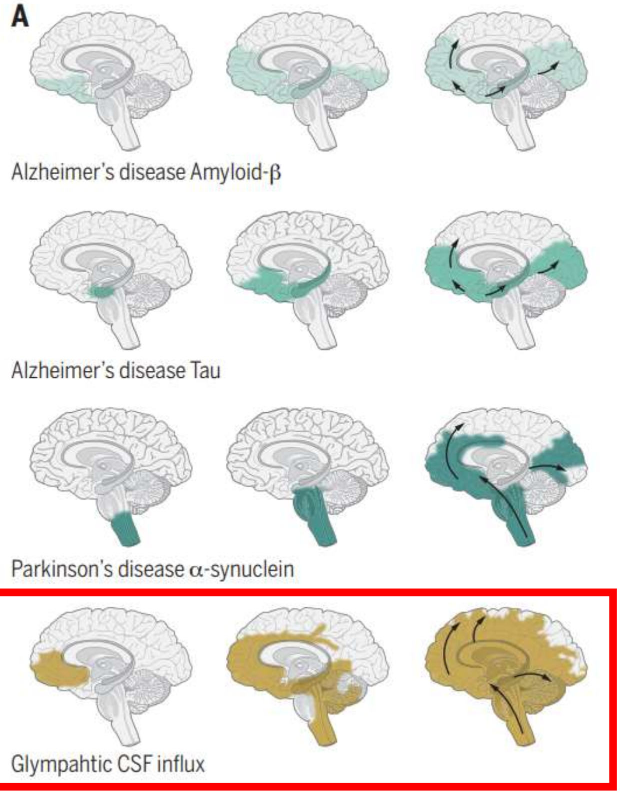
Brain enrichment heavily dependent on tracer enrichment in subarachnoid space.

Protracted process (peak after several hours, even 24 hours)

Ringstad et al., JCI insight, 2018

Tracer distribution *versus* protein aggregation in e.g. AD and PD dementia

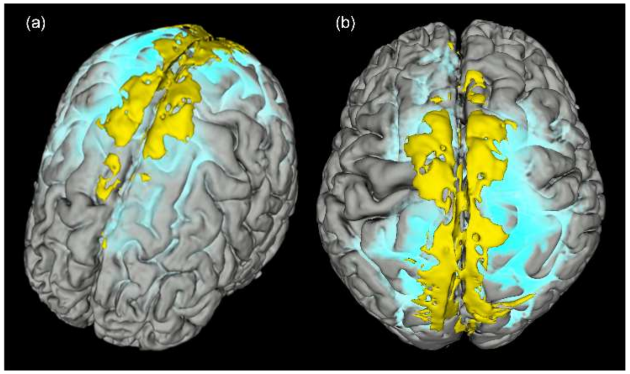




Nedergaard & Goldman, Science, 2020

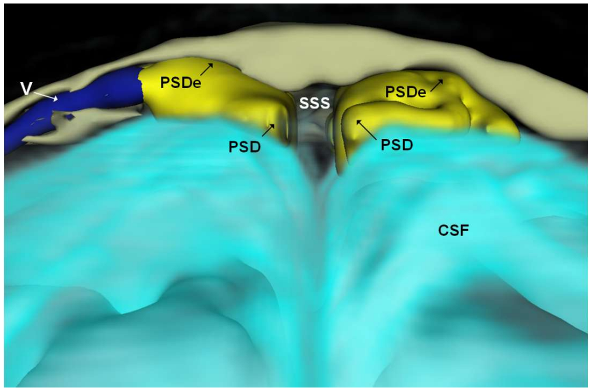
Meningeal efflux routes at vertex

Parasagittale dura (PSD)



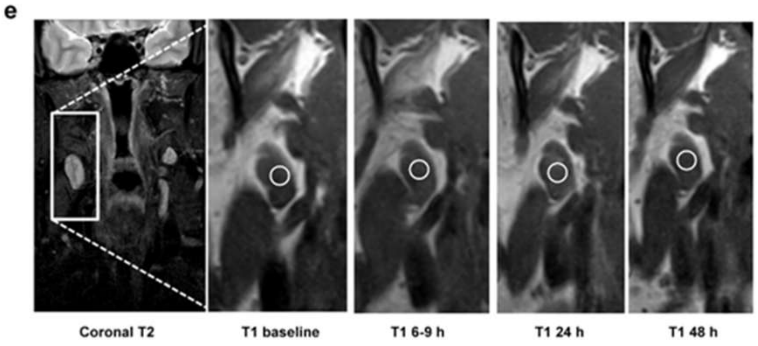
Ringstad & Eide, Nat Comm, 2020

Skull bone marrow



Ringstad & Eide, Brain, 2022

Extra-cranial lymph nodes



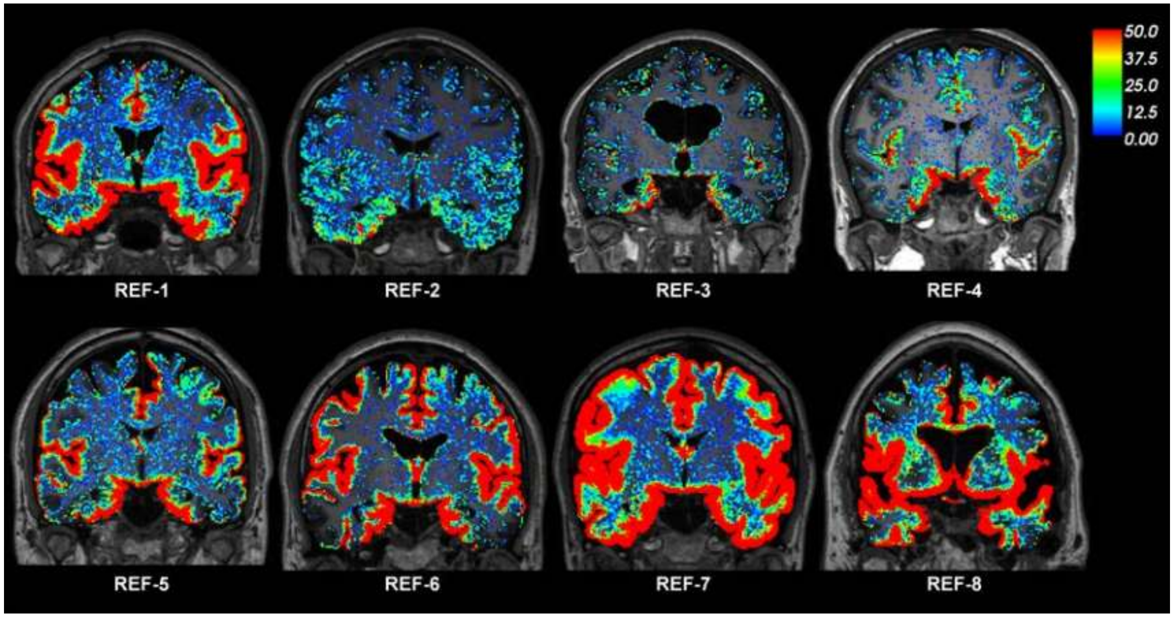
Eide et al., SciRep, 2018

PSD probably no important location for bulk CSF efflux:

1. Enriches late - several hours after peak clearance to blood
2. In individual patients and certain disease categories limited enrichment at vertex

Large inter-individual variations

Glymphatic enrichment at 6 hours



Reference subjects

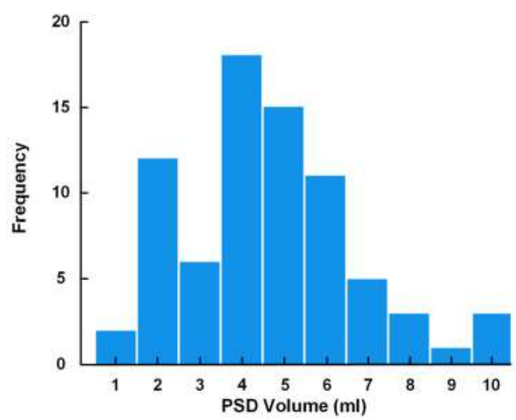
Ringstad et al., JCI insight, 2018

PSD volume varies a lot across patients and disease groups, why?

IIH:

SIH:

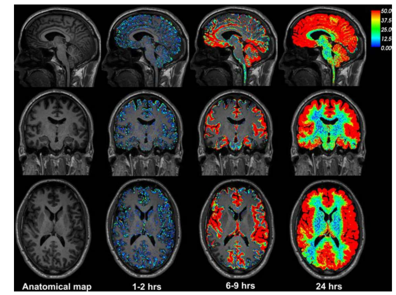
Fig. 1 3D representations of PSD volume estimation. The PSD volume (blue) showed marked variability between patients, here illustrated by **a** small PSD volume in a case with IIH and **b** large PSD in a case with SIH.



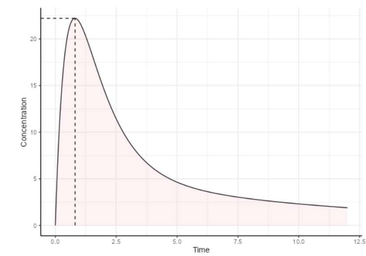
Melin et al., Comm Biol, 2023

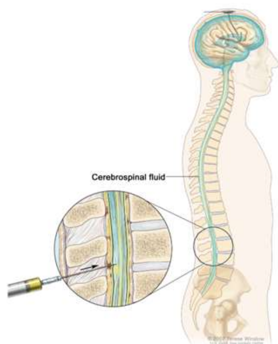
Oslo University Hospital – Rikshospitalet - Since 2015

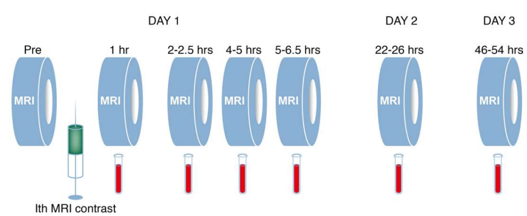
Human glymphatic clearance function → Imaging



Human meningeal lymphatic clearance function → Blood-test



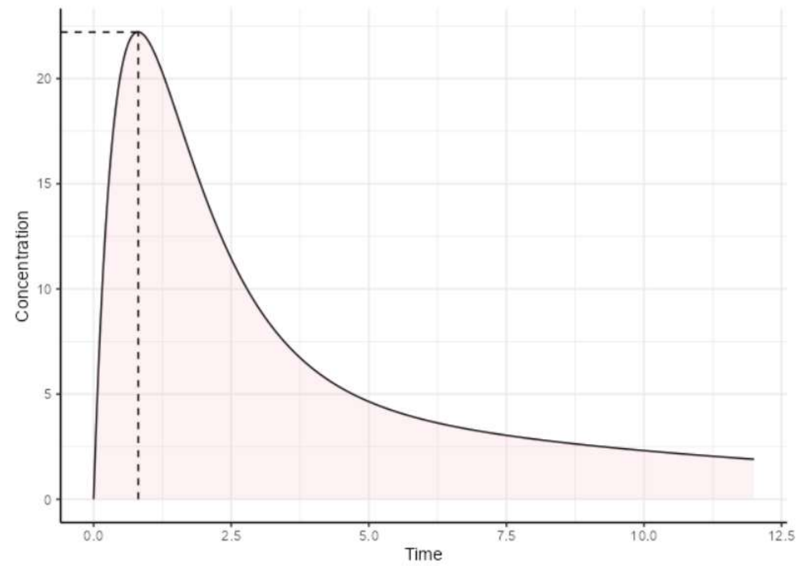




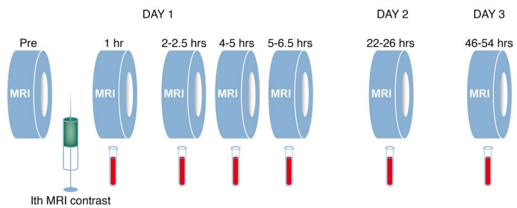
Pharmacokinetic parameters: CSF Elimination Rate

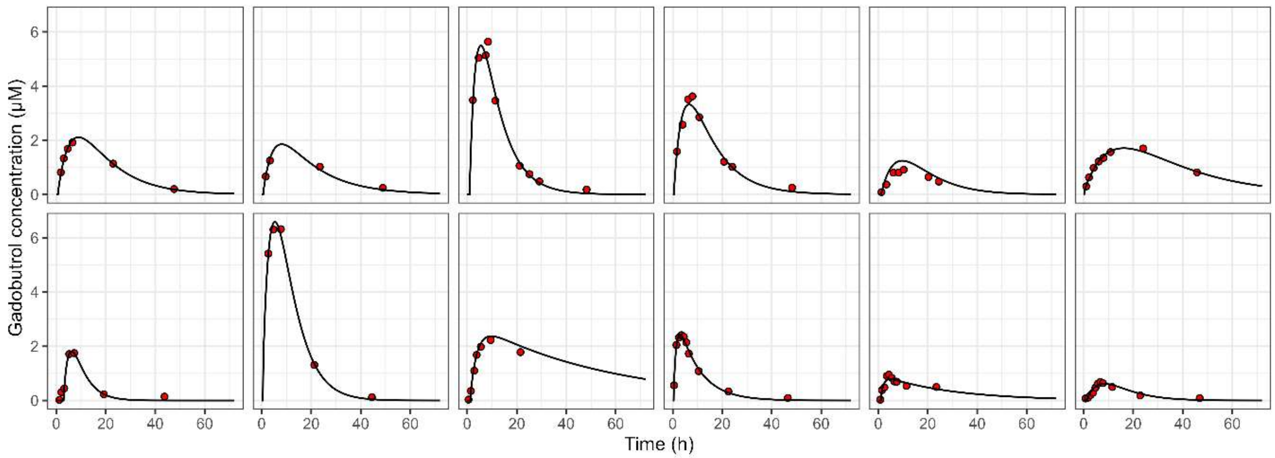
- Absorption half-life
  - Time to 50% of gadobutrol cleared from CSF
- T_{max}
  - Time to peak concentration of gadobutrol in plasma
- C_{max}
  - Peak concentration of gadobutrol in plasma
- T_{lag}
  - Time before absorption to blood from CSF

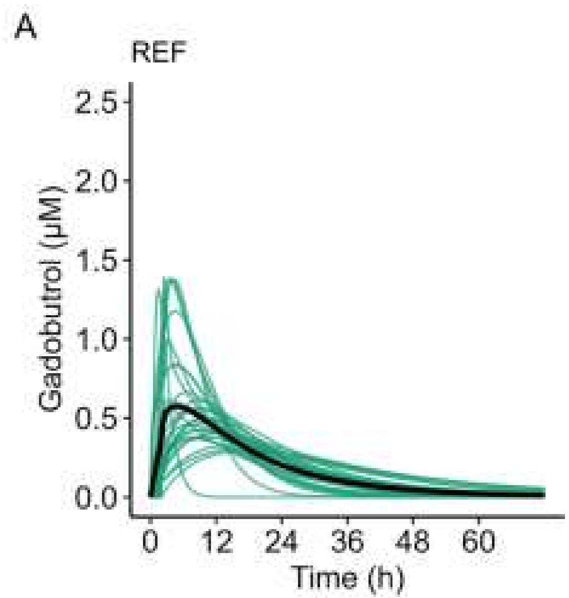
$$T_{1/2,abs} = \frac{\ln(2)}{K_a}$$



Marked inter-individual variation in CSF elimination rate





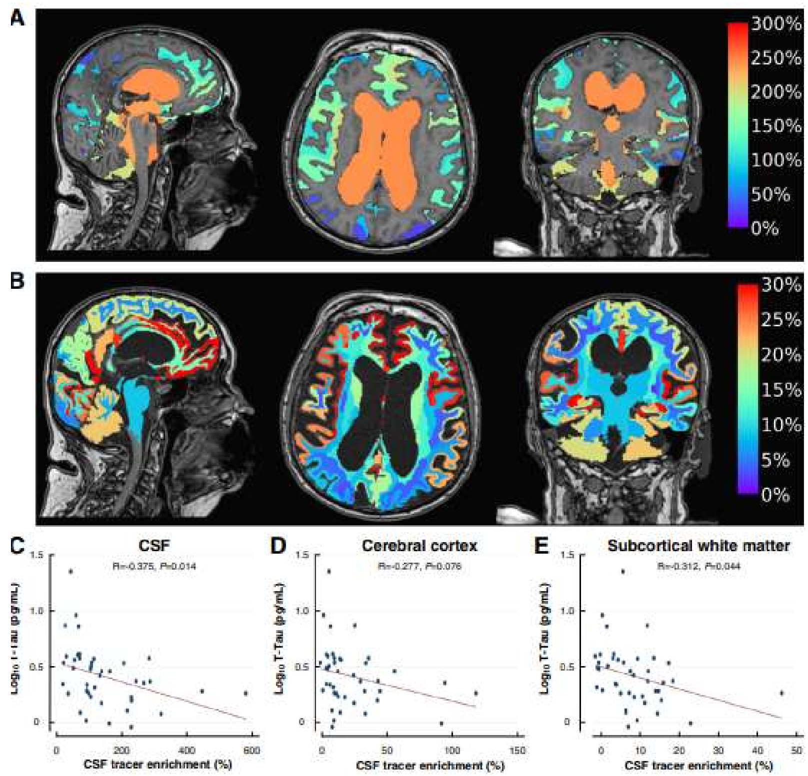


Most of the tracer (~60%?) is cleared to blood at spinal level

Hovd et al., FBCNS, 2022

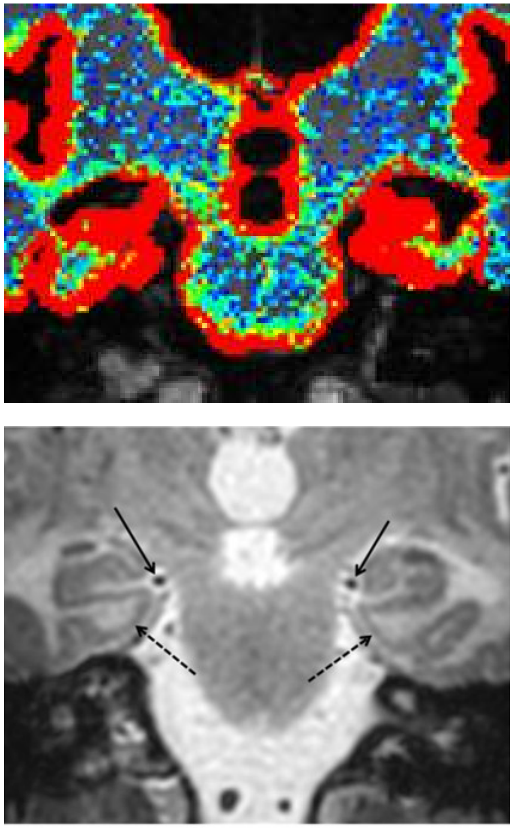
Implications of large inter-individual variation in CSF Elimination Rate for cognitive function?

Variables of CSF elimination rate associate with plasma biomarkers (amyloid/tau)

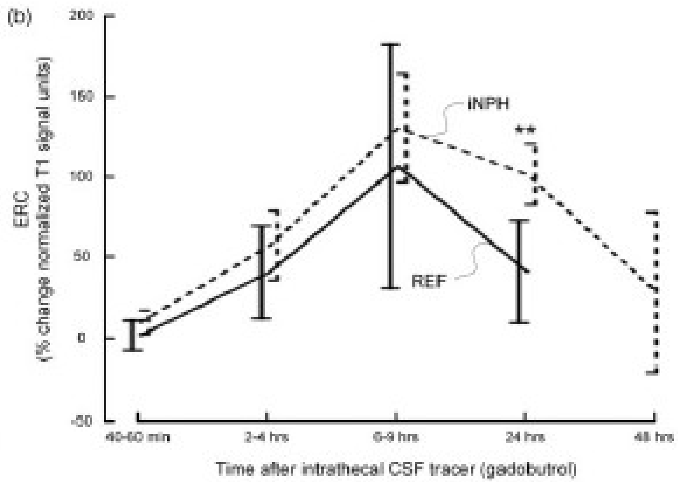


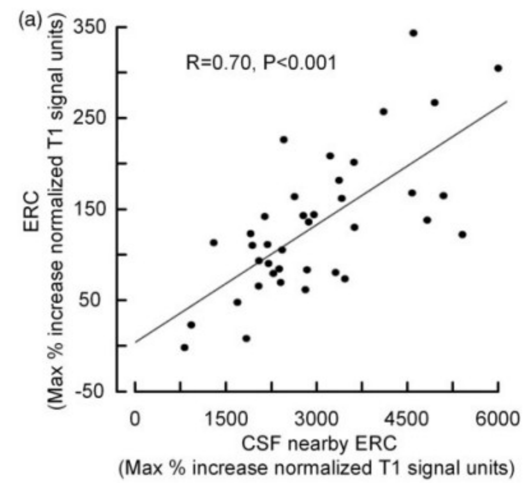
Eide et al., Nature Comm, 2023

Entorhinal cortex (ERC)



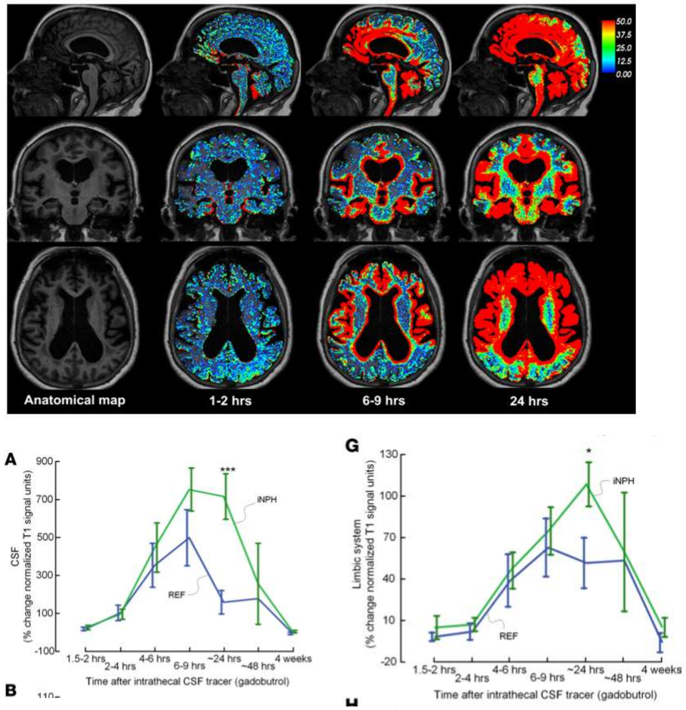
iNPH: Idiopathic normal pressure hydrocephalus



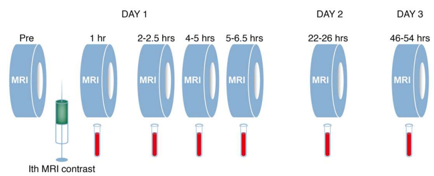


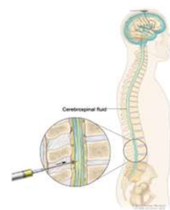
Eide et al., JCBFM, 2019

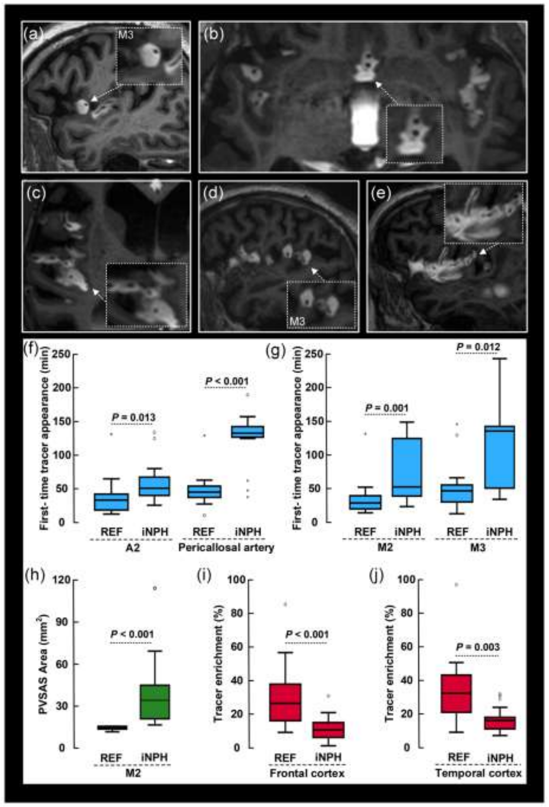
Idiopathic normal pressure hydrocephalus (iNPH): Delayed clearance



Ringstad et al., JCI insight, 2018

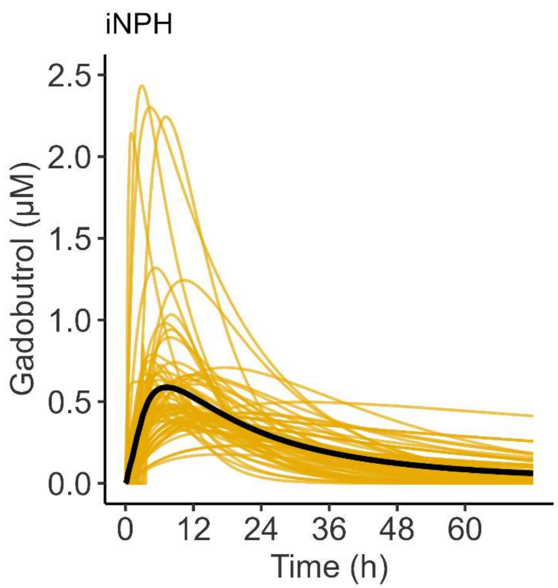






Eide & Ringstad et al., Nature Comm, 2024

iNPH: CSF Elimination Rate



	REF	iNPH
Number of subjects	28	63
$T_{1/2, abs}$ (h)	4.57 ± 3.31 (72%)	4.15 ± 3.07 (74%)
T_{max} (h)	7.49 ± 4.09 (55%)	9.85 ± 5.4 [a] (55%)
C_{max} (µM)	0.70 ± 0.38 (54%)	0.67 ± 0.48 (72%)
T_{lag} (h)	0.74 ± 0.67 (91%)	1.16 ± 0.77 [a] (66%)
$AUC_{0-\infty}$ (µM h)	12.58 ± 2.55 (20%)	18.49 ± 8.24[c] (45%)

Hovd et al., FBCNS, 2022

Summary

1) In humans there are large inter-individual variation in the glymphatic transport as well as the CSF Elimination Rate

2) CSF Elimination Rate differs depending on underlying diagnosis and was impaired in subjects with a disease characterized by cognitive decline.

3) CSF Elimination Rate probably is modifiable and therefore of interest to study in relation to cognitive failure?

Glymphatic imaging & modeling – University of Oslo

Per Kristian Eide, MD, PhD
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