



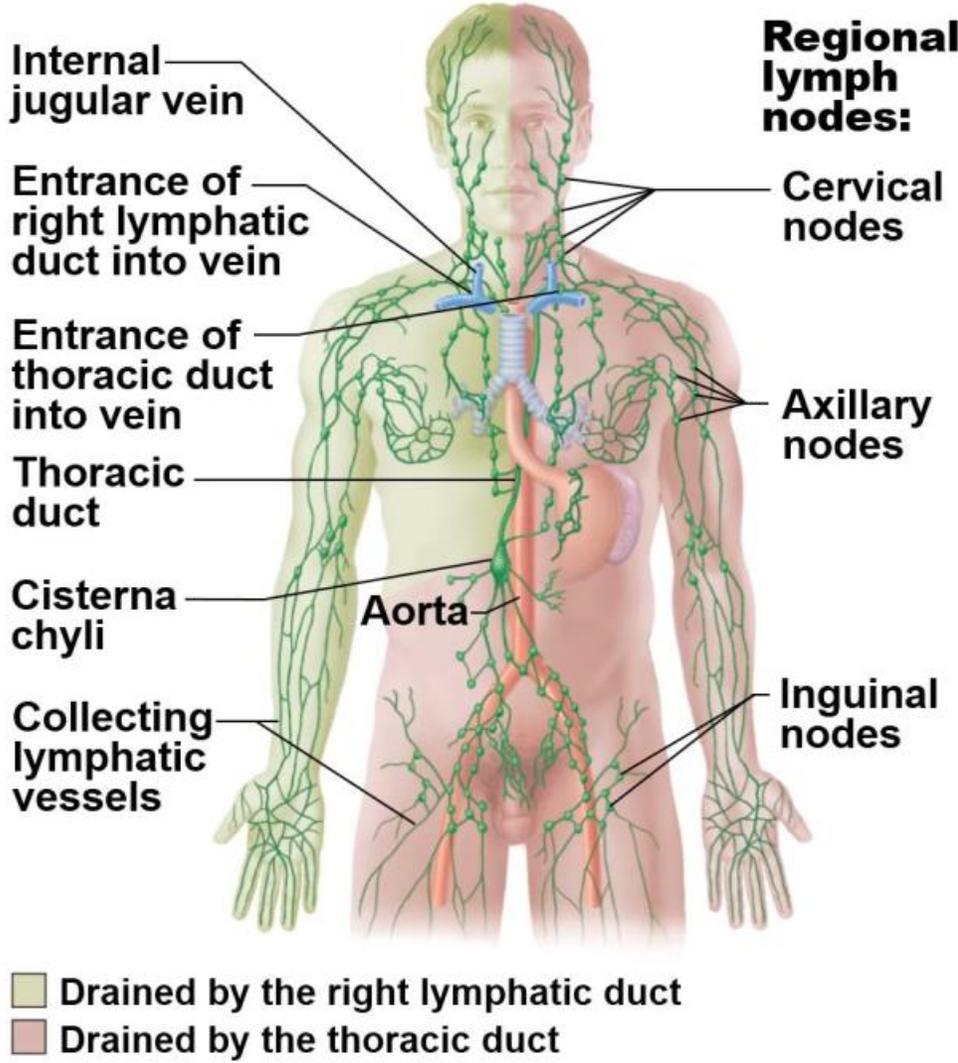
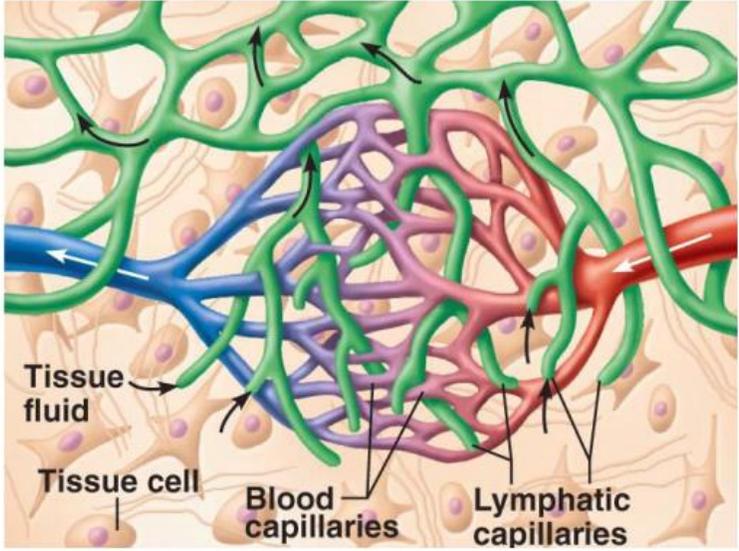
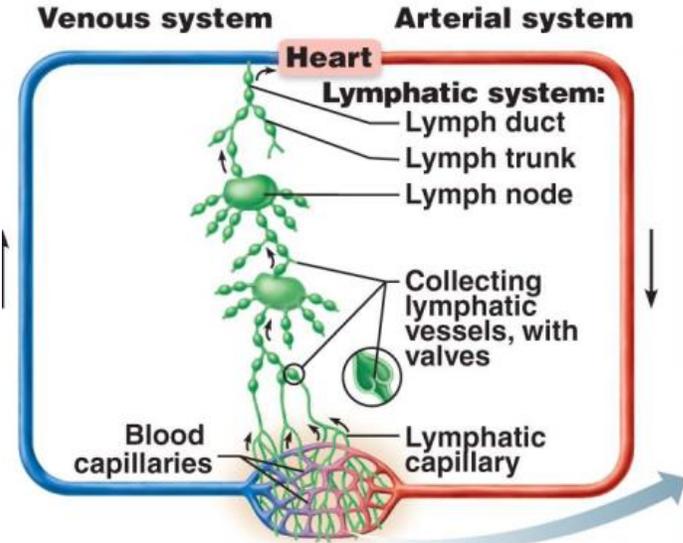
The role of lymphatic system in neurodegeneration

Yong-Won Shin, MD

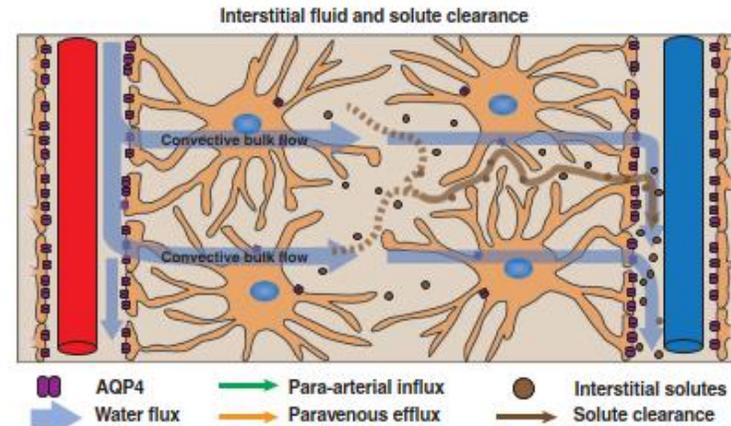
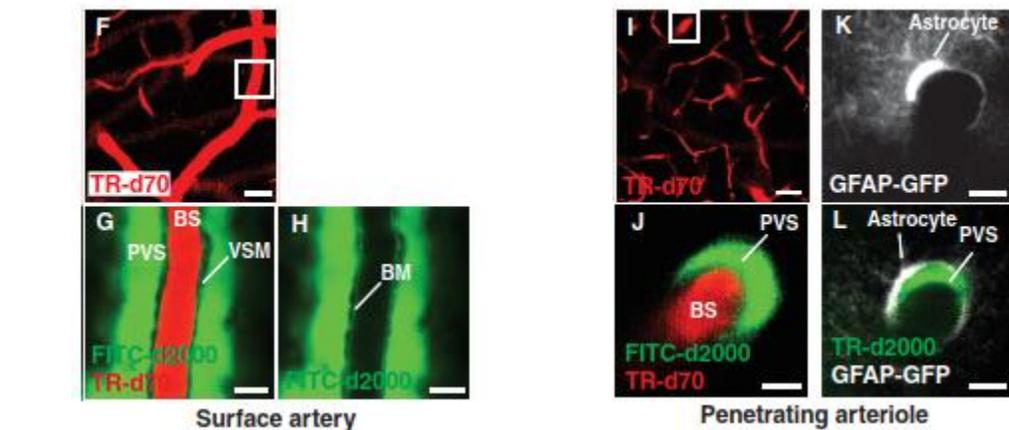
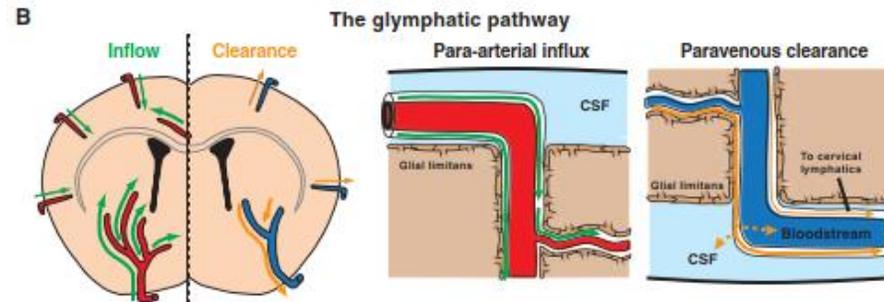
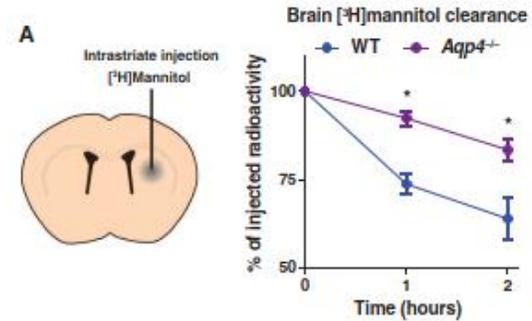
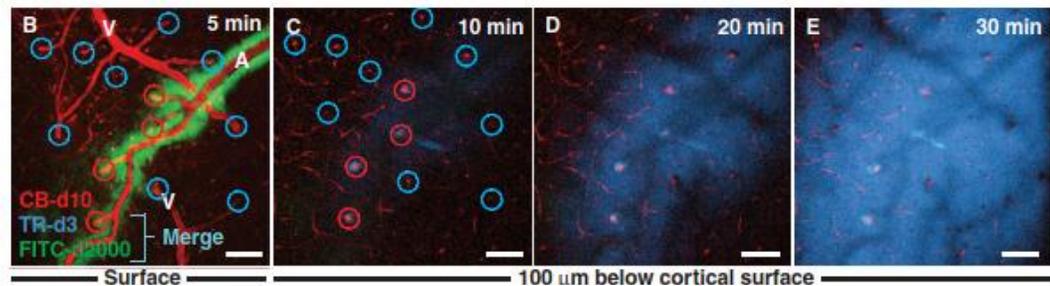
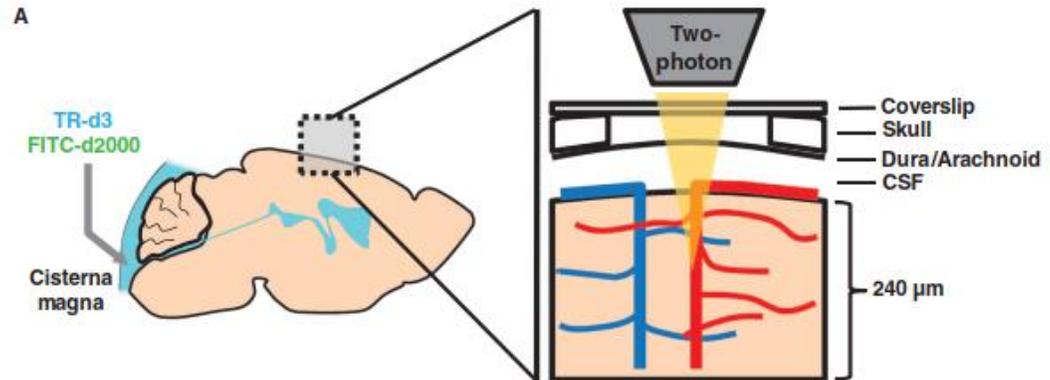
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Lymphatic system

- Returns fluids that leaked from capillaries back to blood
- Monitors for presence of foreign material and initiates defensive countermeasures when necessary



Glymphatic system



Description of lymphatics in dura mater

Rami, qui ex linguae superficie, ac substantia nascuntur, diversos formant truncos, quorum aliqui in ramos divisi ad duas glandulas juxta sanguineorum decursus positas, atque ex his ad glandulas circum divisionem jugularis interpositas producuntur, reliqui verò huc directè concurrunt.

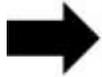
Ex larynge, ex parte inferiore pharyngis, ac superiore glandulae thyroidae adeunt glandulas, quae aut inter jugulares & glandulam thyroidem, aut supra jugulares jacent, vel directè, vel aliis prius trajectis glandulis, quae cartilagini thyroidei, atque cricoidi accumbunt. Caetera ab ima glandulae thyroidae sede, vel coadunantur in glandulas tracheae supernè accumbentes, ut cum iis conficiantur, quae ex pulmonibus, & ex glandula juguli huc adveniunt, ac dein truncis communibus sub jugularem internam in glandulas inferiores colli se immittant, vel directè antè aut ponè jugularem internam ad has glandulas tendunt.

Durae matris lymphatica sanguineorum decursum sequuntur, ac cum iis per foramen spinosum exeunt ex cranii cavitate, dein iis copulantur, quae ex musculis pterigoideis permanant, ac glandulas petunt divisioni jugularis internae appositas. Aliqui trunculi inter laminas durae matris juxta sinum longitudinalem se demergunt. Dura meninge a cranio avulsa postquam lymphatica per injectionem coloratam in vasa sanguinea glutine absque colore intumescere, multi se offerunt trunculi, qui in externa ipsius superficie resecti apparent. Ex hoc autem conjiciendum puto eos immitti in cranii foraminula ut per extimam ipsius superficiem egrediantur. Verum ut haec vascula glutine absque colore repleantur necesse est, ut sanguineorum injectio optimè cedat, quod hic loci perrarè evenire expertus sum. Attamen id quandoque mihi contigit ut horum truncos juxta arterias, ac venas meningae oculo vitris adjuto usque ad foramina spinosa sequi potuerim, atque hinc in glandulas usque, quae adjacent jugularis internae divisioni.

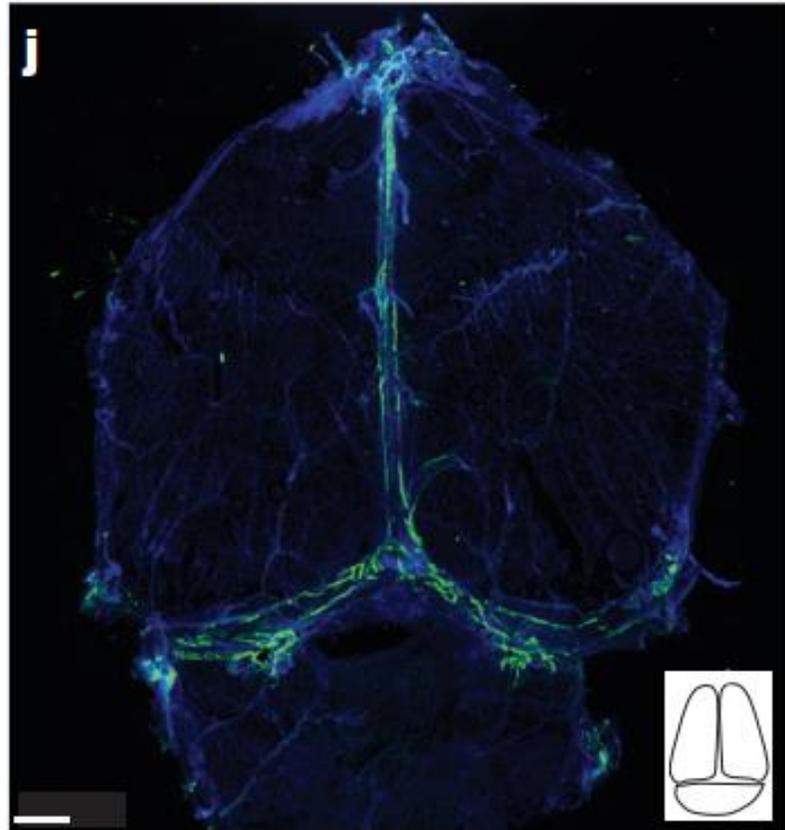
Lymphatica in cerebri superficie simili modo glutine absque colore repleta vidi. Cum in cadaveribus sanguinis effusiones inveniebantur nonnumquam repleta conspexi vascula quaedam, quae ex nodulis, cursu aliisque qualitatibus ita lymphatica aemulabantur, ut, si quid longa docet experientia, ejusdem esse indolis vocare in dubium nequiverim. Sed exilissima haec vascula maxima ex parte cum inter laminas durae matris una cum venis sanguineis se demergant juxta sinus longitudinales ductum oculis tandem se subducunt. Idque iis evenit, quae ex hemisphaeriis in cerebri basim reclinantur cum circa carotides coadunantur. Haec autem tam excellunt tenuitate ut ipsa numquam injicere potuerim mercurio.

Sed injeci alia vascula satis ampla in aracnoide sita, quae aut aere, aut glutine post

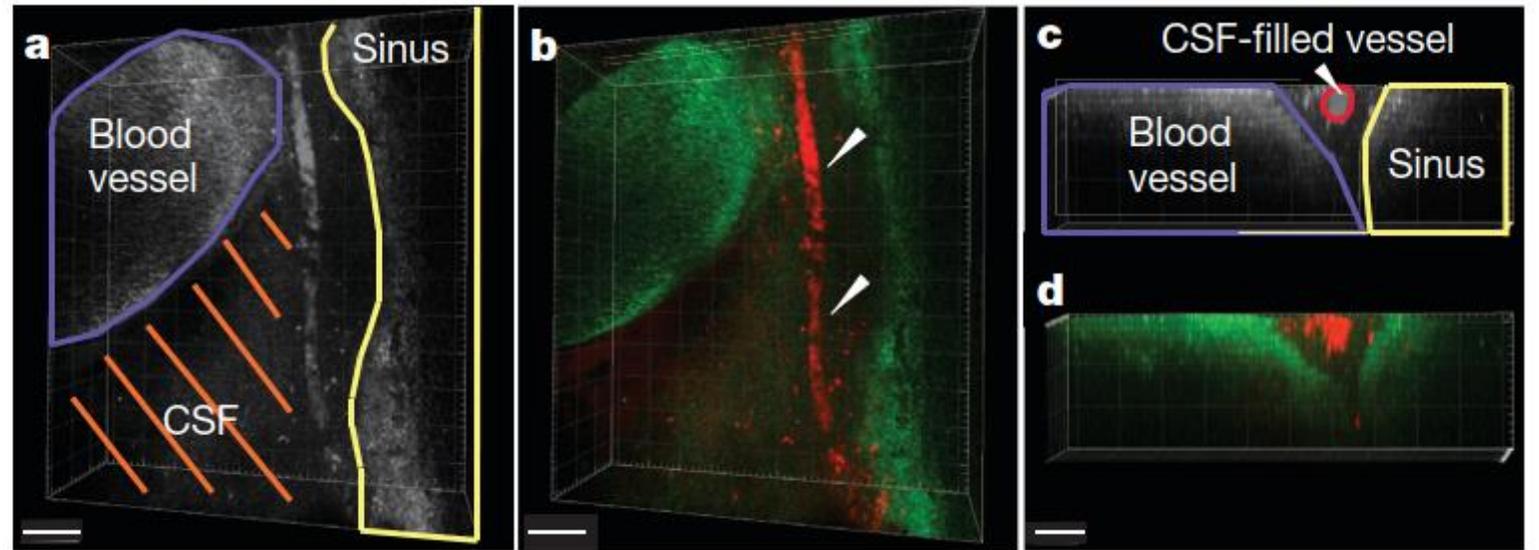
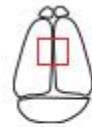
- The presence of lymphatics in human dura mater has been described by Mascagni (1787)
- More recent reports (Lecco, 1953; Li et al. 1996) have also confirmed this historic observation



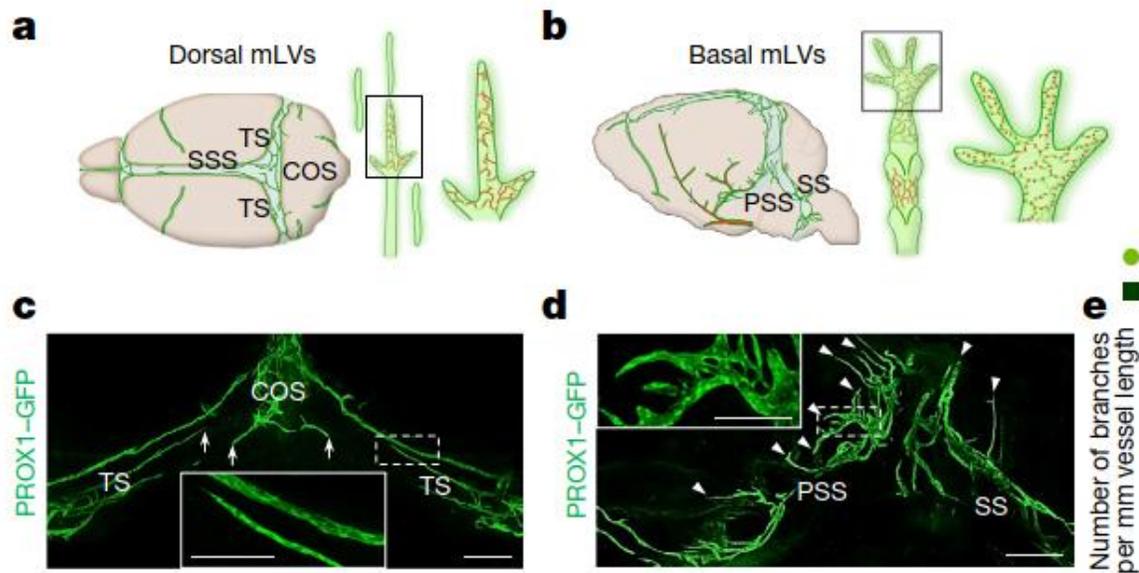
Visualization of Meningeal lymphatics (re-discovery)



Lyve-1 DAPI

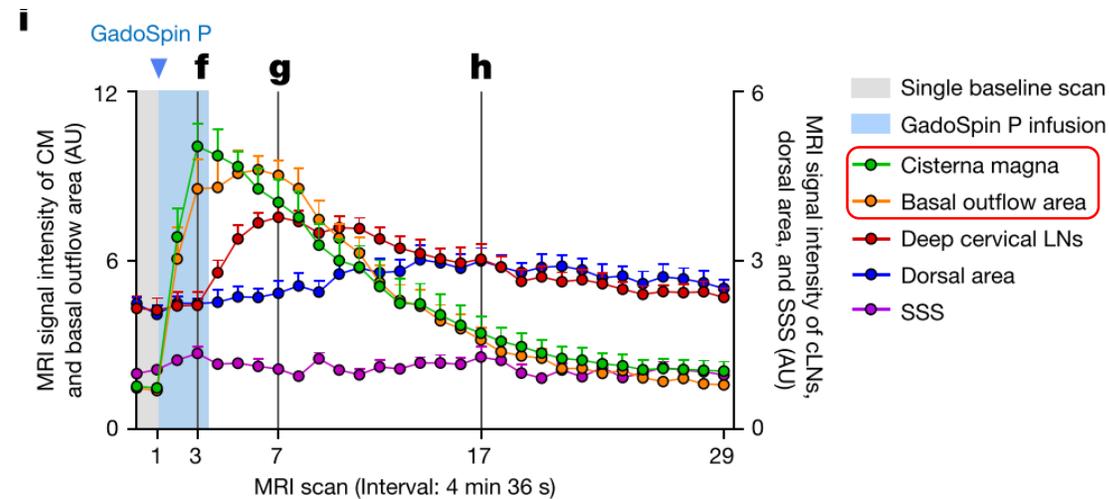


QDot 655 (ICV) Fluorescein (IV)

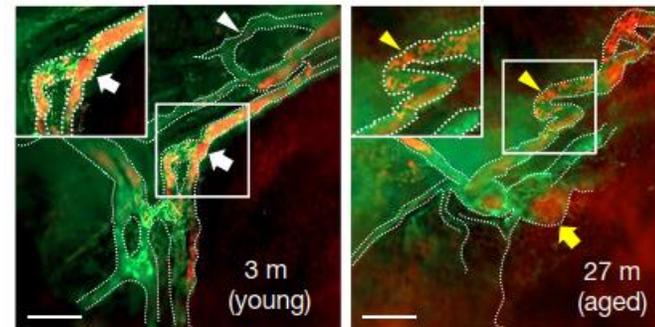


- Small diameter
- Largely discontinuous vascular structure
- Clustered within dural fold

- Larger diameter
- Abundant protruding capillary branches with blunt end

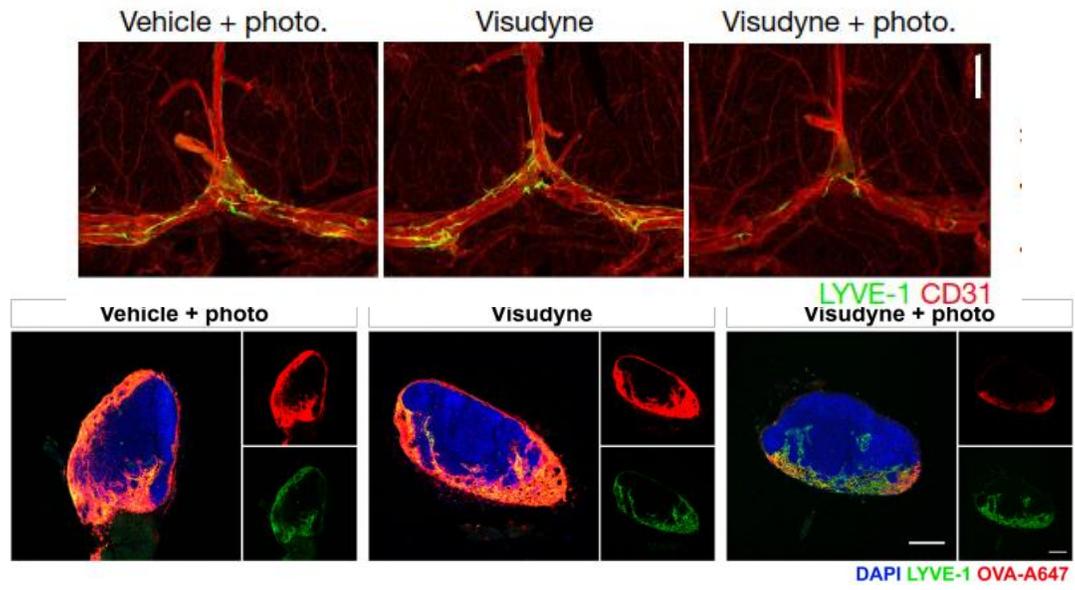
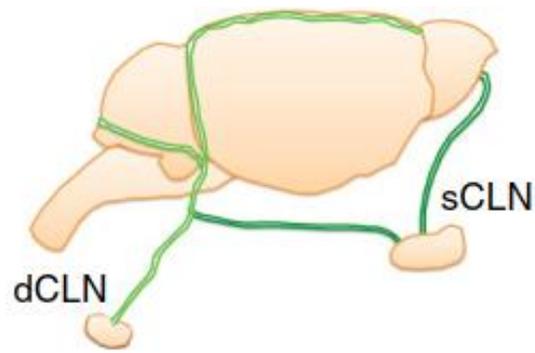


CSF drains preferentially through the basal outflow

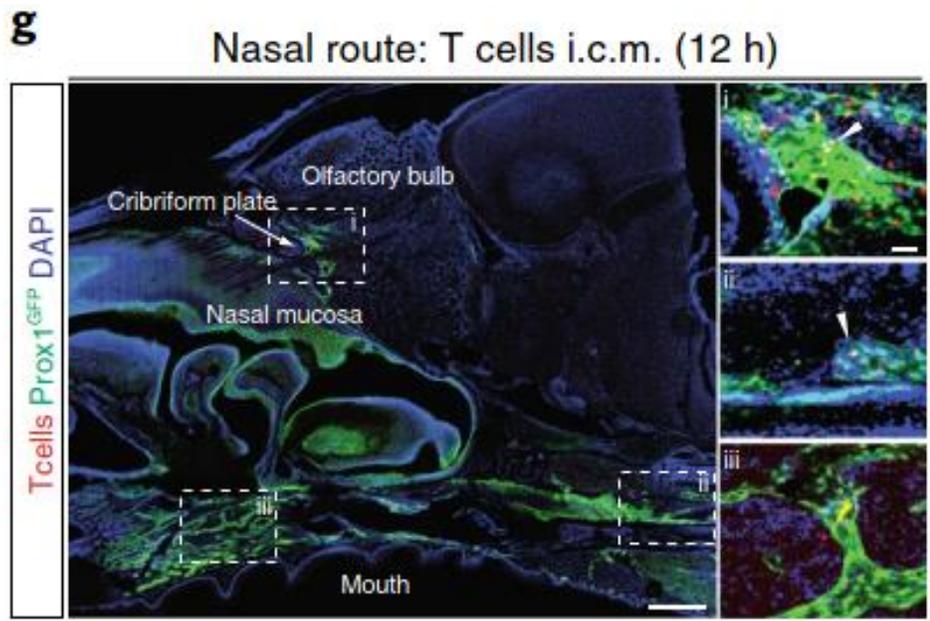


Aged basal mLVs are tortuous and dilated

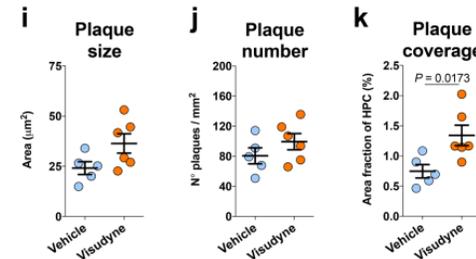
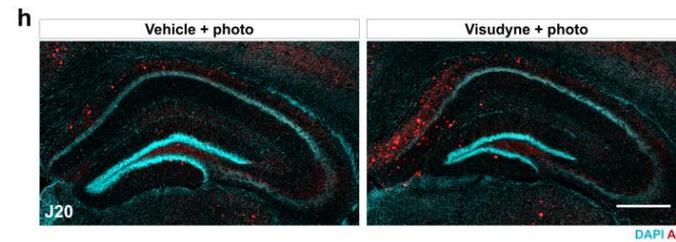
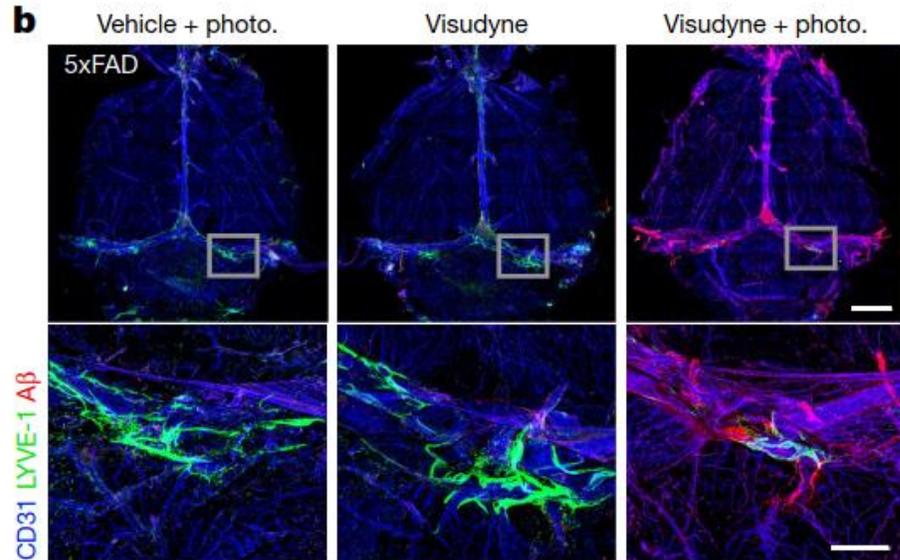
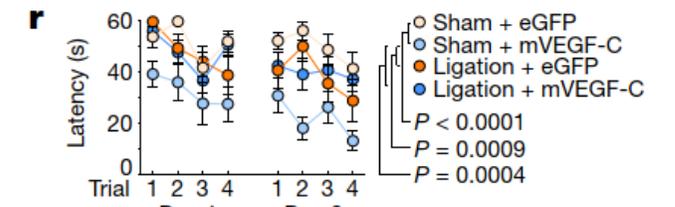
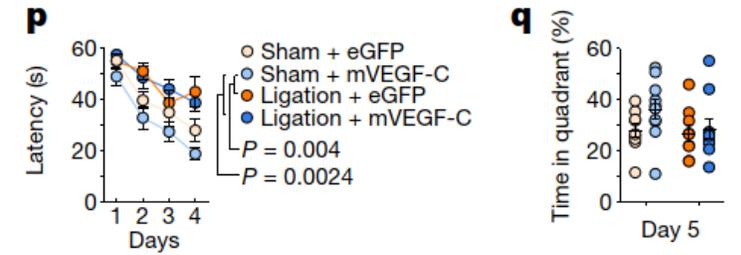
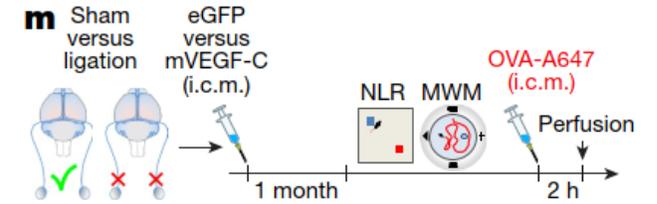
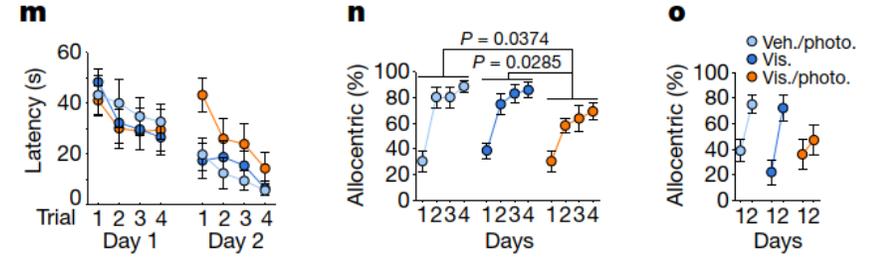
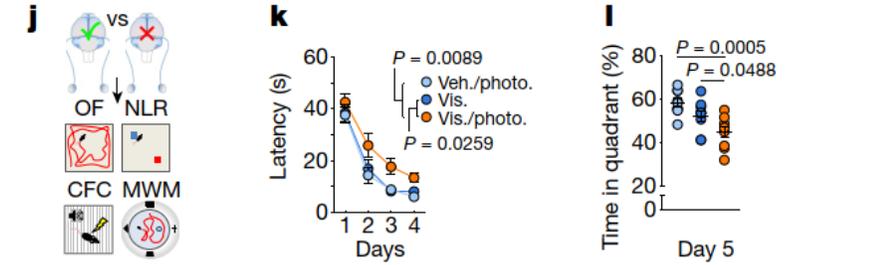
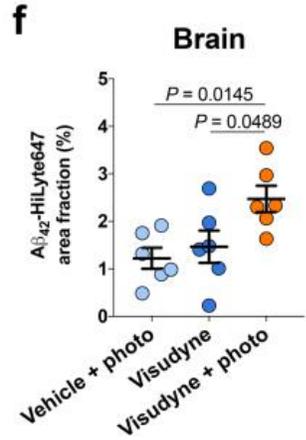
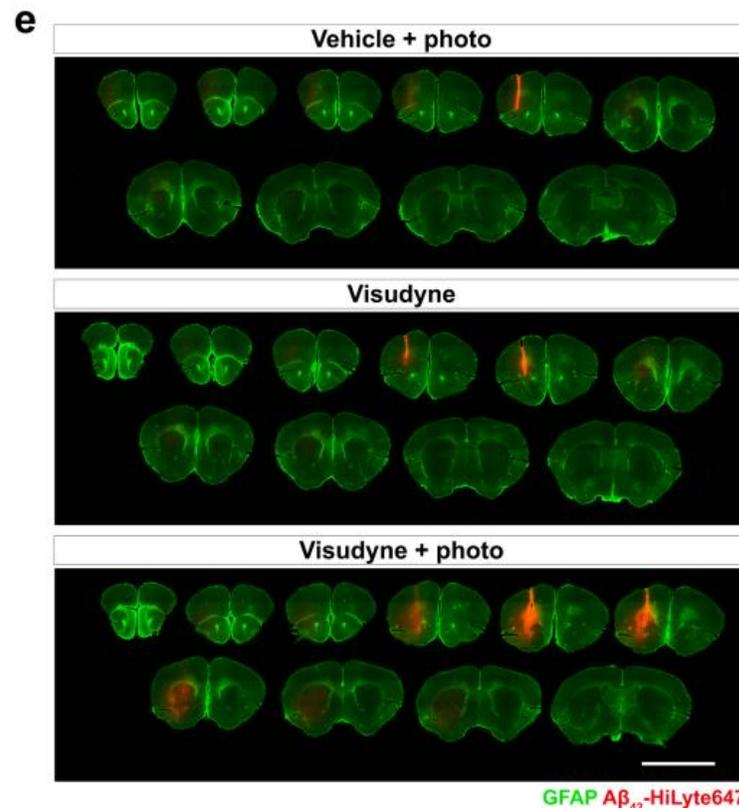
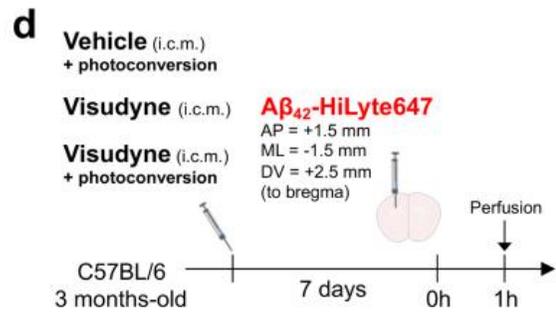
QD705 LYVE-1

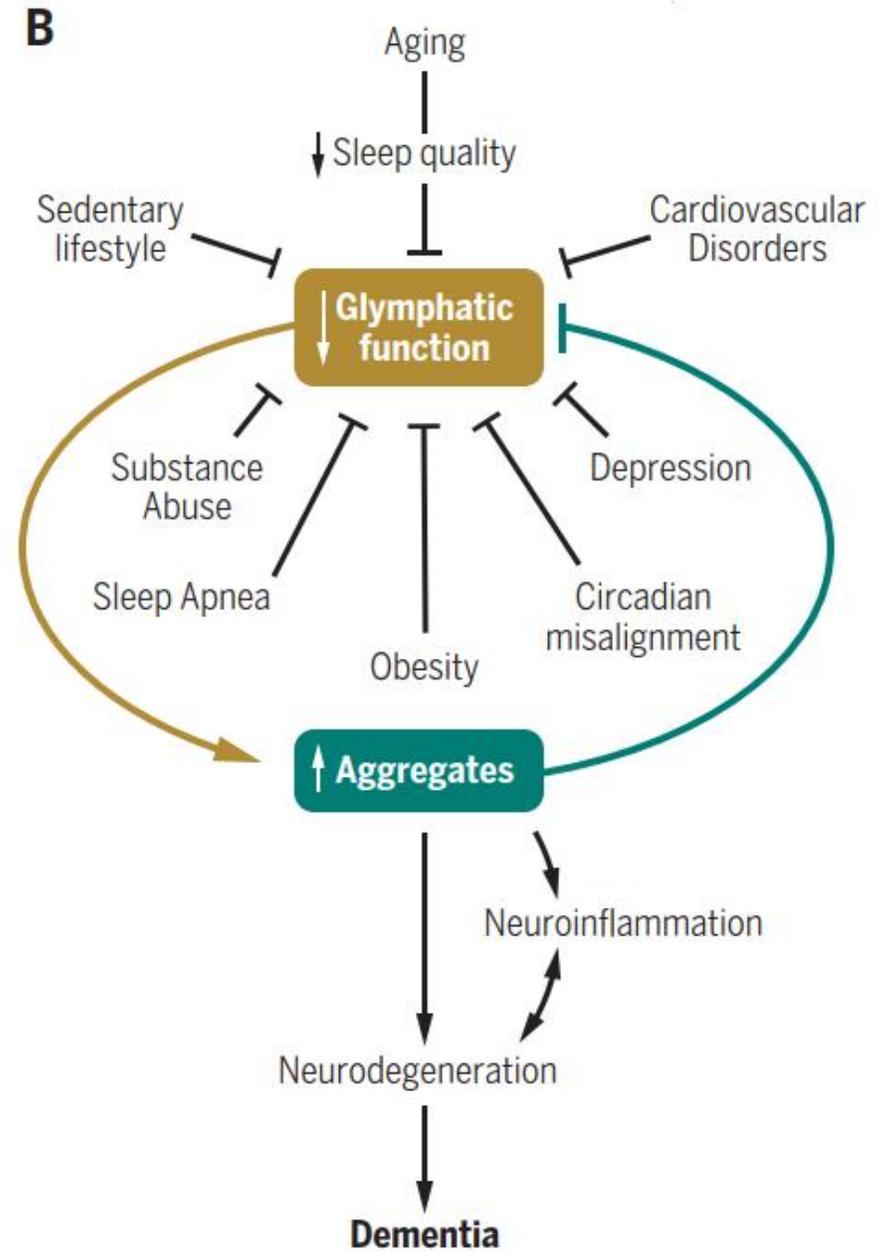
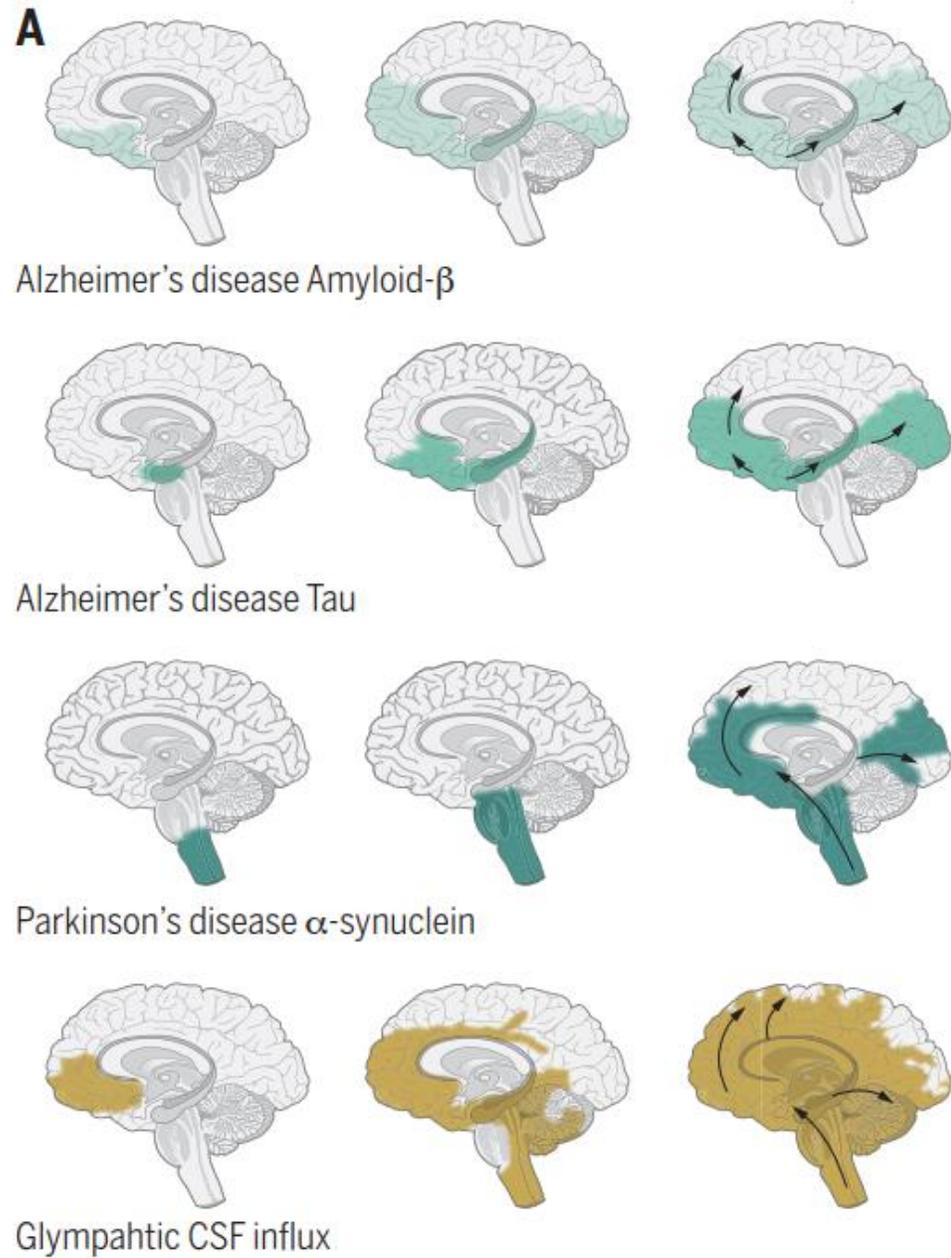


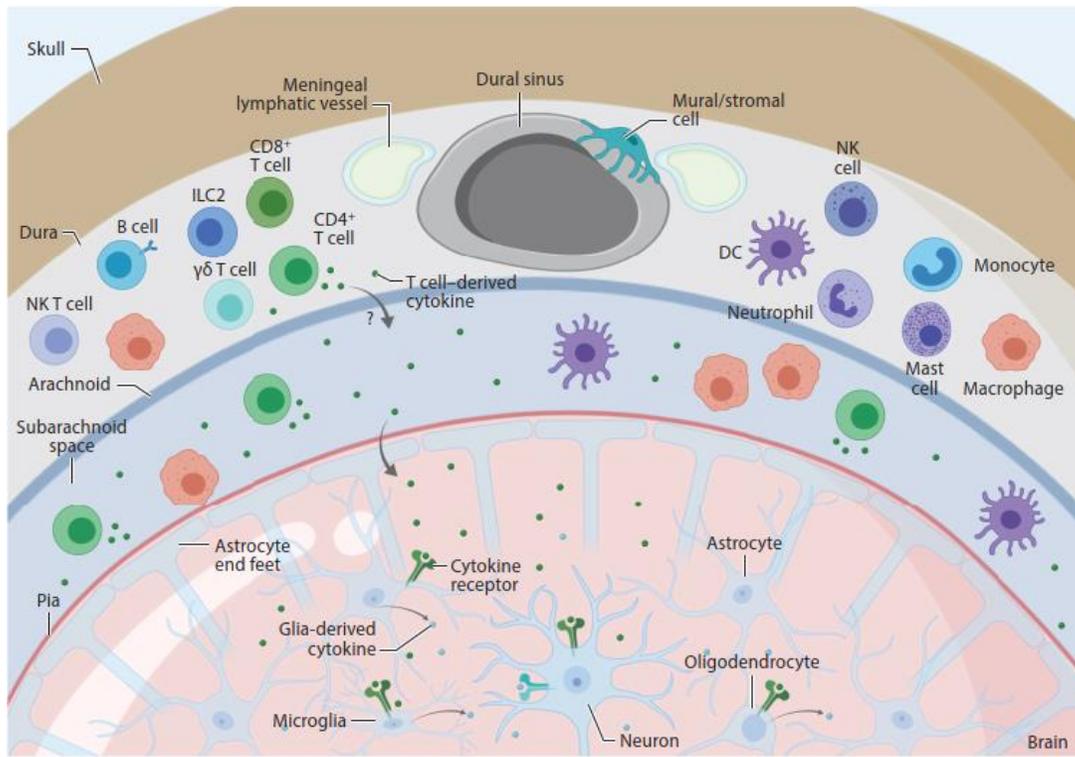
Da Mesquita et al. Nature 2018



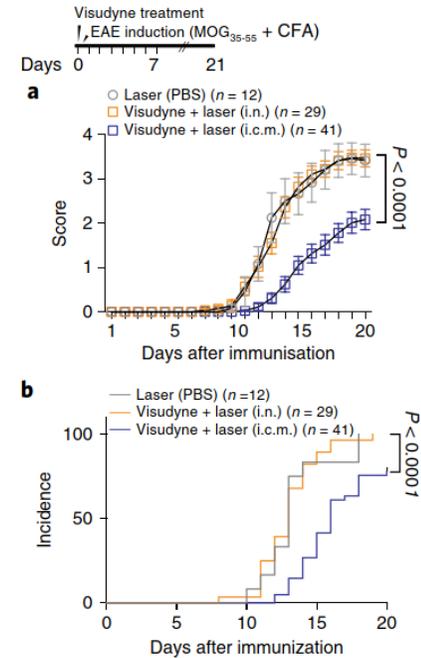
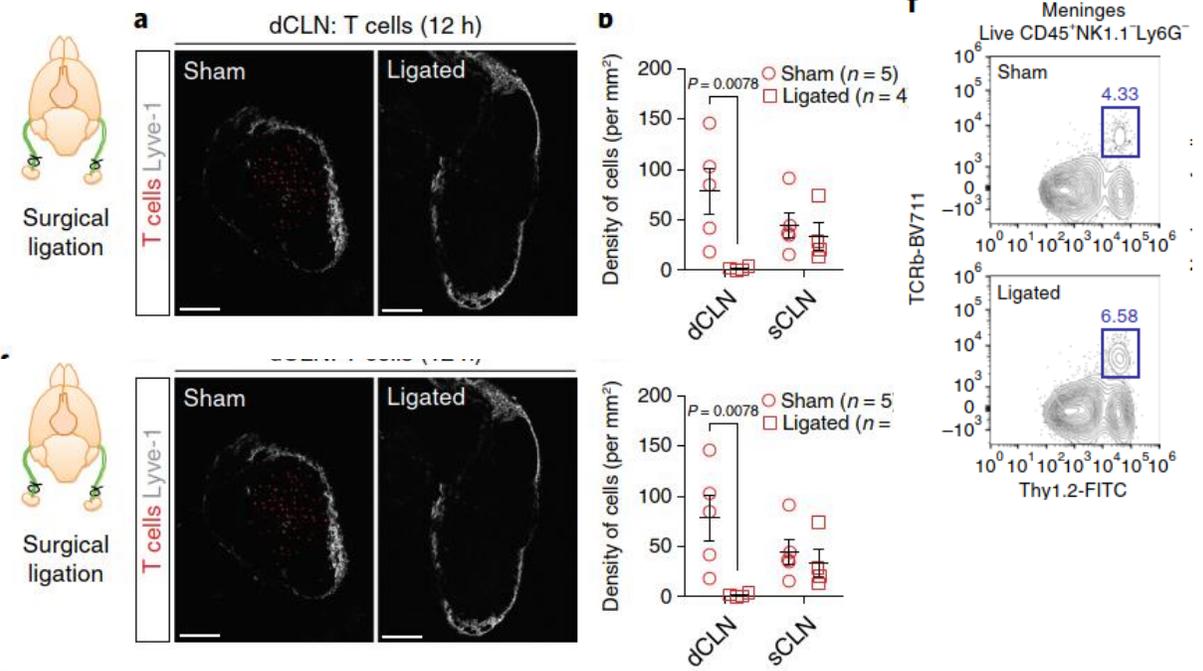
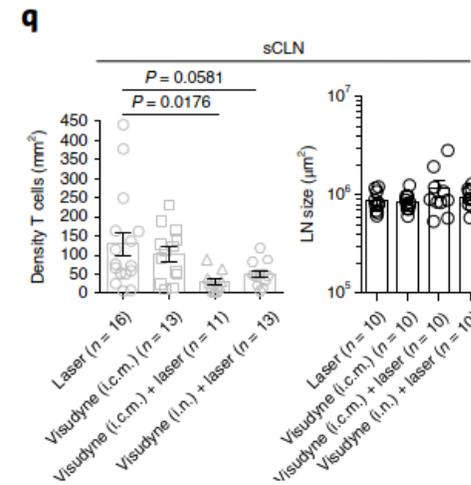
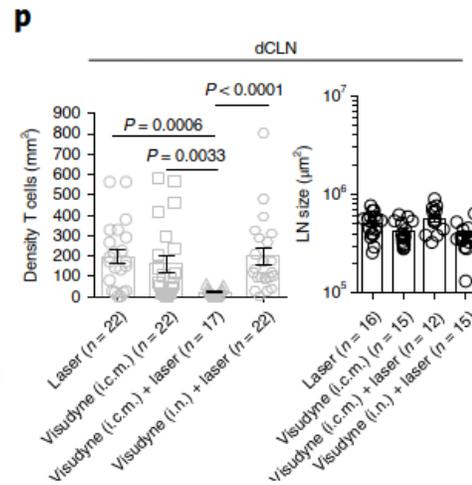
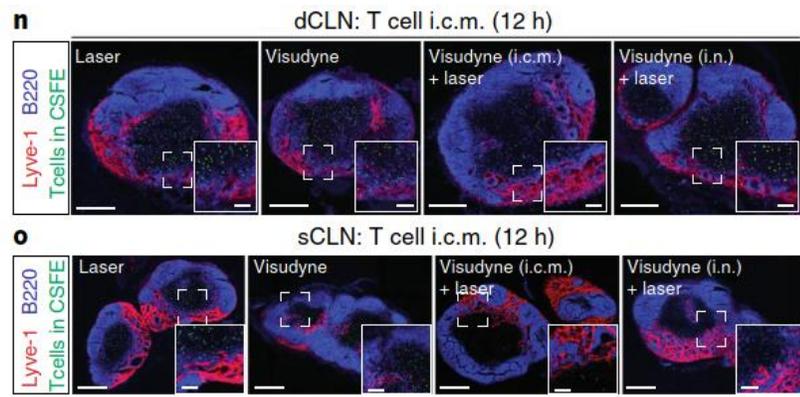
Louveau et al. Nature Neurosci 2018







Lima et al. Ann Rev 2020



Louveau et al. Nature Neurosci 2018

Meningeal lymphatics summary

- Meningeal lymphatic vessels are positioned along the dural sinuses
- Drain brain-derived soluble waste to deep cervical lymph nodes
- Meningeal lymphatics mediate waste removal from the brain and connect the brain with the peripheral immune system
- Cerebrospinal fluid is primarily drained via lymphatics and not into the dural sinuses
- Lymphatic dysfunction with aging or other condition could be associated with neuroinflammatory and neurodegenerative diseases

Association of meningeal lymphatic neuroinflammation

- Surgical excision of CNS-draining lymph nodes reduces relapse severity in chronic-relapsing experimental autoimmune encephalomyelitis

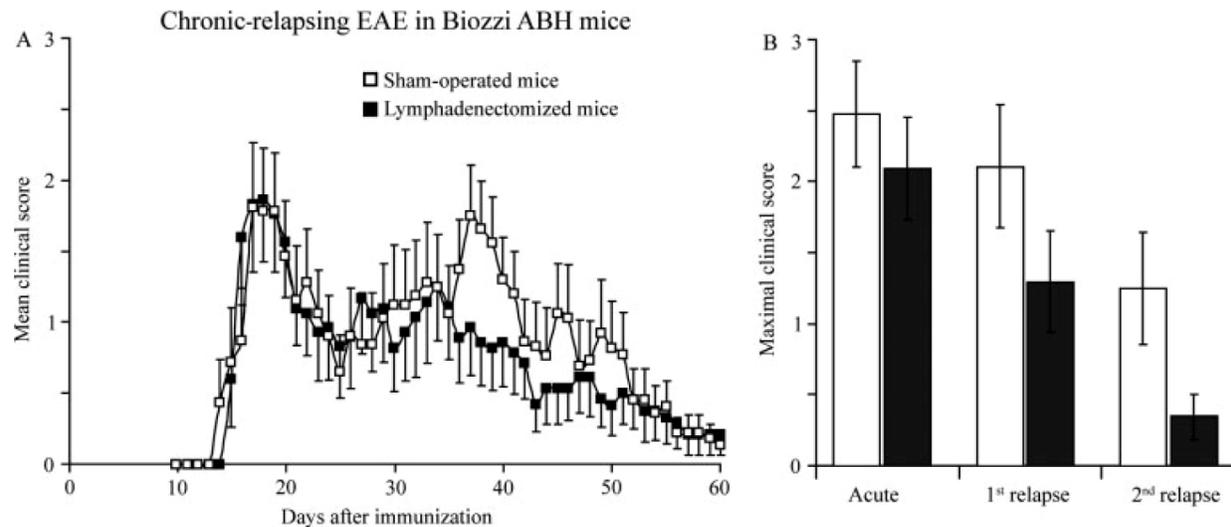


Table 1. Clinical features of lymphadenectomized and sham-operated mice

Clinical feature	Relapsing EAE		Acute EAE		Chronic EAE	
	Sham	LN	Sham	LN	Sham	LN
Incidence	16/19 (84%)	15/22 (68%)	5/6 (84%)	5/6 (84%)	9/10 (90%)	6/10 (60%)
Day of onset acute disease	19.7 ± 1.6	20.1 ± 2.0	12.0 ± 1.3	12.6 ± 1.4	12.0 ± 0.8	11.2 ± 1.3
Day of onset first relapse	32.3 ± 2.5	33.0 ± 2.5				
Day of onset second relapse	40.5 ± 2.5	49.2 ± 3.7				

