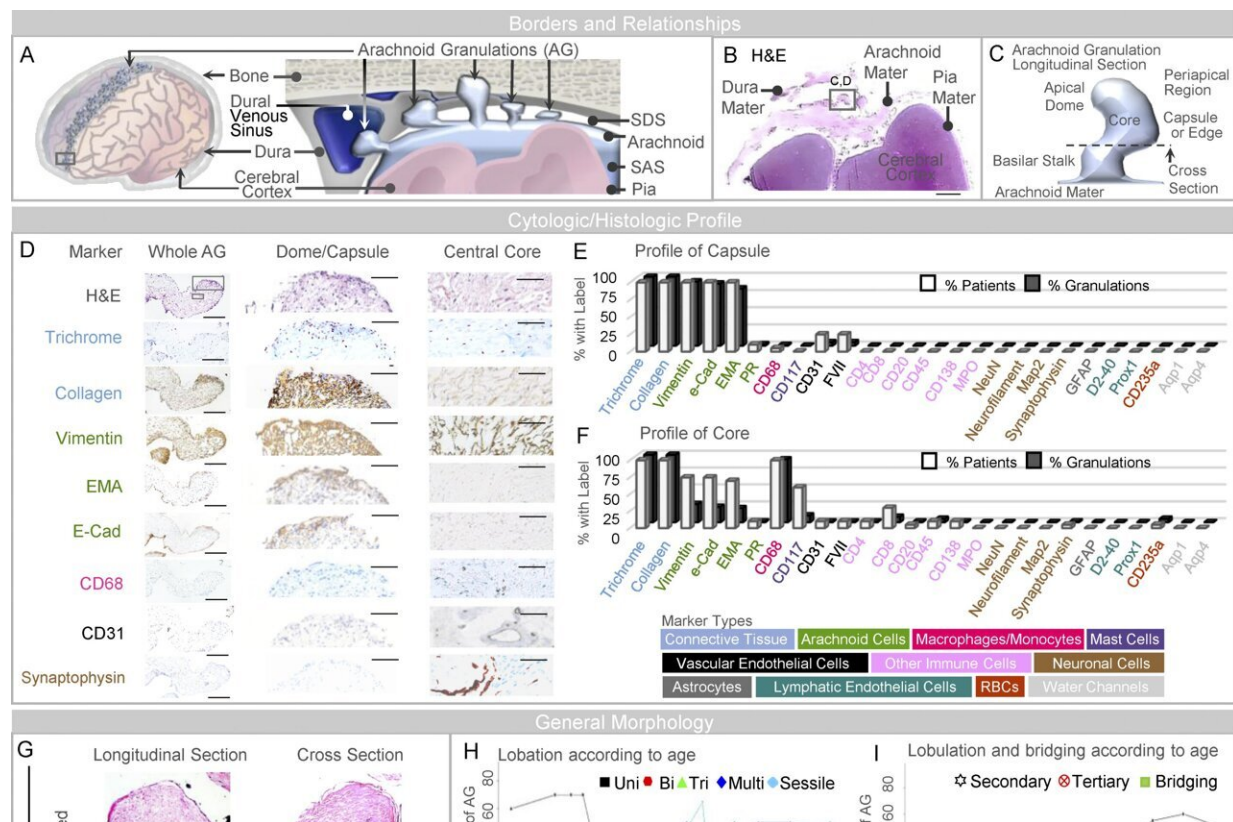


Research shows how the human brain drains fluid

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AG abut dura mater and are heterogeneous in size, form, and composition. (A) A schematic depicts the general arrangement of AG in the superior parasagittal frontal brain region. (B) Similarly, low-power image of an H&E-stained frontal pole section illustrates basic meningeal relationships. (C) Schematic depiction of a single granulation, shown in longitudinal orientation, summarizes its general morphology which includes a capsule or edge, core, basilar stalk or neck, and apical dome region. (D) Intermediate-power images further illustrate labels of an isolated granulation, including dome capsule and central core regions. (E and F)

Labeling profiles of each granulation are summarized from all patients at the granulation capsule (or edge) and inner core, respectively, in E and F; cell marker types used for initial screening are shown in the lower panel. (G) As illustrated, AG are pedunculated (or polypoid) and unilobed, bilobed, trilobed, or multilobed; or are sessile and plaque-like in morphology; some granulations exhibit secondary and tertiary lobulations with or without apical bridging. (H and I) The number of morphologies and the number of lobulated and bridged granulations are summarized by age in H and I, respectively. (J and K) Maximum diameter is shown according to age and lobe type in J and K, respectively. (L and M) Stalk diameter is shown according to age and lobe type in L and M, respectively. Scale bars: (B) 500 μm ; (D [left]) 200 μm ; (D [middle and right]) 50 μm ; (G) 20 μm . Bi, bilobed; EMA, epithelial membrane antigen; Multi, multilobed; PR, progesterone receptor; Tri, trilobed; Uni, unilobed. Dotted lines in G represent the approximate orientation of cross-section shown on the right-hand side. Data represent findings in 400 frontal pole granulations from 20 decedents and are from more than two independent experiments. Credit: *Journal of Experimental Medicine* (2022). DOI: 10.1084/jem.20220618

New research at RUSH is changing current understanding of the brain by revealing new knowledge about structures involved in cleansing it of fluids and waste with a steady fluid stream.

This system is called the brain's lymphatic system—how fluid escapes the brain and drains into thin tubes—which allows for the circulation and removal of brain waste fluid.

The research is led by Rupal Mehta, MD, a physician-scientist and associate professor at RUSH University Department of Pathology and RUSH Alzheimer's Disease Center.

Differing from current medical literature, the research shows that fluid escapes the [human brain](#) and drains into channels in the outer tissue layer that surrounds it. There are three thin layers of meningeal tissues in the

outer leaflike covering that protects the brain.

This discovery is published online and in the February 2023 printed issue of the *Journal of Experimental Medicine*. New studies of this previously unknown area may help shed possible new clues about various brain diseases and what role it may play.

"In this study we describe arachnoid granulations, which are small mushroom-shaped outpouchings of the brain's inner covering, as outlets that connect the brain plumbing system with adjacent lymphatic channels," Mehta said.

"When leaving the brain, fluid and debris is carried away into arachnoid granulations. Therefore, granulations may teach us a whole lot regarding what's going on in the brain, and how the brain functions and cleanses itself. Future studies on granulations may potentially help explain a range of brain diseases and lead to new therapeutics."

The researchers found that a significant proportion of granulations border on bone and lymphatic channels or thin tubes, rather than the brain's great veins as previous medical literature suggests. Medical literature describes arachnoid granulations as structures at the brain surfaces that drain passively and exclusively into the brain's great veins called dural venous sinuses.

Before it was widely recognized that the brain had a lymphatic system, there was no reason to question arachnoid granulation structure. But with other recent discoveries in the field, Mehta and the RADC team decided to investigate for themselves.

The authors analyzed more than 400 granulations across a number of brain specimens. Using a variety of microscopes and tissue preparation techniques, they examined the delicate tissues employing state-of-the art

methods.

In recent years, scientists have described the glymphatic system, a fluid irrigation system within the brain that cleans out toxins. In combination with recently discovered lymphatic vessels present in the brain's outer membranes, this system drains noxious materials from the brain.

This glymphatic system has been shown to carry brain waste from the brain, along the skull and to lymph nodes in the neck regions where the toxins are removed by the immune system. Several studies now show that this brain drainage system plays important roles in a range of diseases. However, the fluid outlets, or region of glymphatic-lymphatic connection, in humans has been a mystery.

In the new study, the author Trishna Shah and colleagues used high-resolution microscopes with special staining and MRI techniques to characterize the shapes and arrangement of various parts of these granulation tissues in persons who varied in age. The authors found that the internal framework of granulations consists of slivers of collagen that form a delicate sponge-like mesh or sieve, and contains different types of immune cells. The outer capsules of the granulations were also found to be perforated.

These findings differ from what is published in historical and modern-day textbooks. Moreover, the structure of granulations suggests that fluid and immune material percolate through the sponge-like tissues to escape onto the other side of the brain coverings, where the lymphatic vessels and bone are located.

"These structures appear to act like a filter that trap brain waste material and immune cells. They share several morphological features of peripheral [lymph nodes](#)," Mehta said. "The findings suggest that the human brain has a well-developed and built-in mechanism for filtering

and removing brain waste."

The research shows how overlooked these tiny structures have been, but Mehta says that special high-power microscopes that were not widely available a few decades ago helped visualize the structure. Until now, detailed analyses using the newer microscopes have not been conducted. The functions of arachnoid granulations have not been fully understood by scientists and physicians.

For hundreds of years, they have been thought of as passive tissues and the brain coverings have been regarded as membrane-bound seals. Previously, it was not fully recognized that arachnoid granulations contain immune elements or communicate with spaces in the overlying tissues.

"This area of the brain is rarely analyzed and is overlooked on brain autopsy exams," said Julie Schneider, co-author and director of the Alzheimer's Disease Research Center. "Given that arachnoid granulations undergo significant aging changes, it could indicate a role in brain diseases like Alzheimer's disease."

In addition to unexpected location, shapes and arrangement of these parts, the authors also found a distinguishable age-associated change in arachnoid granulation content. The observations are important because they may fill in important gaps in what physicians and scientists know about brain aging and the unique ins and outs of the [brain immune system](#).

Moreover, the findings could have importance for diseases associated with aging, such as stroke, trauma, and various forms of dementia. The authors hope that the discovery will translate into new insights for patients who suffer from neurological diseases. Mehta said that in future studies, the RADDC team will study associations between arachnoid

granulation deterioration and amyloid build-up in the brains of people with Alzheimer's disease.

More information: Trishna Shah et al, Arachnoid granulations are lymphatic conduits that communicate with bone marrow and dura-arachnoid stroma, *Journal of Experimental Medicine* (2022). [DOI: 10.1084/jem.20220618](https://doi.org/10.1084/jem.20220618)

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