PURSUIT OF ZΩH — THE WEEKLY

This Week in

Neuroscience

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THIS WEEK

A barrier that imports, and a virus that makes you sneeze

The blood-brain barrier imports proteins, a coronavirus enzyme triggers sneezes, one splice fix restores synapses in ALS-model neurons, and a 1.2-million-person study maps pain genes.

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01

BLOOD-BRAIN BARRIER

The blood-brain barrier is also a delivery dock

The blood-brain barrier is usually described by what it keeps out.[1] A Gladstone Institutes team led by Andrew Yang tagged plasma proteins in mice and followed them: the healthy barrier sampled 191 and let 92 into brain tissue.[1,2] Most were made in distant organs, especially the liver, and each tended to reach a particular cell type.[1,2] APOA1 crossed via the receptor SR-B1 and was handed to the astrocyte transporter ABCA1, an Alzheimer's risk gene.[1] In early-stage 5xFAD model mice, APOA1 import fell, and boosting liver APOA1 rescued synaptic and behavioral deficits.[1]

> WHY IT MATTERS
>
> *It recasts the barrier as a selective supply line, and suggests a failing import route, not only a leak, could be an early step in Alzheimer's disease.*[1,2]

CAVEAT *All of this work was done in mice; whether human Alzheimer's begins this way is still a hypothesis.*[2]

[1] doi:10.1016/j.cell.2026.10.039 · [2] eurekalert.org

92

plasma proteins the healthy mouse blood-brain barrier let into brain tissue, of 191 it sampled

SOURCE 1

ON THE ROAD?

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6-minute episode, read aloud: the same four stories, written for the ear. Stream it, or download the MP3, from the Neuroscience page.

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02

SENSORY NEUROSCIENCE

A coronavirus enzyme taps the sneeze nerves directly

Sneezing, coughing and pain during a respiratory infection start with nociceptors, the sensory neurons that detect harmful stimuli in the airways.[3] A UC Berkeley team led by Diana Bautista found that one SARS-CoV-2 enzyme, the papain-like protease PLpro, activates these neurons directly, in mice and in human nociceptors grown from stem cells.[3] Given to mice, PLpro triggered sneezing, coughing, acute pain and release of the neuropeptide CGRP in the airways.[3] Activation needed both the enzyme's cutting activity and the host channel TRPA1.[3] Infection with a mouse coronavirus also caused TRPA1-dependent sneezing.[3]

WHY IT MATTERS

It names a viral enzyme and a host ion channel as candidate targets for COVID-19 symptoms, not yet tested as treatments.[3]

CAVEAT *Mouse and cell-culture work; an earlier version was posted as a bioRxiv preprint on 11 January 2024.*[3,4]

[3] doi:10.1016/j.neuron.2026.10.017 · [4] doi:10.1101/2024.01.10.575114

MECHANISM

Virus makes papain-like protease (PLpro)

↓

Its protease activity excites nociceptors

↓

Host TRPA1 channel is required

↓

Sneeze, cough, pain and CGRP release

03

ALS AND DEMENTIA

One splice fix restores synapses in ALS-model neurons

In amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), the RNA-binding protein TDP-43 is often lost from the nucleus, and hundreds of transcripts are then spliced wrongly.[5] A University College London team led by Pietro Fratta found that neurons lacking TDP-43 stay structurally intact while their synaptic communication badly breaks down.[5] Correcting just one faulty splicing event, in UNC13A, was enough to rescue it.[5] Splice-switching antisense oligonucleotides restored spontaneous and evoked vesicle release, release probability and network synchrony in human neurons, and corrected the splicing in a humanized mouse model.[5]

WHY IT MATTERS

The authors call the strategy relevant to roughly 97% of people with ALS and roughly 50% of people with FTD with TDP-43 pathology.[5]

CAVEAT *The synaptic rescue was measured in human neurons in culture; in mice, the paper reports correction of the splicing.*[5]

[5] doi:10.1038/s41586-026-11256-2

97%

share of ALS patients (roughly) for whom the authors say UNC13A splice correction is relevant

SOURCE 5

04

GENETICS OF PAIN

A 1.2-million-person scan finds 343 places pain lives in the genome

Chronic pain is common worldwide, yet its genetics are only partly mapped.[6] A Philadelphia team from the Crescenz VA Medical Center and the University of Pennsylvania combined 1,235,695 people of European ancestry from three biobanks in a genome-wide association study of multidimensional pain.[6] They found 343 independent loci, 92 of them new for pain.[6] Run separately, the analysis found 115 loci in males (n = 583,066) and 12 in females (n = 241,266).[6] Mendelian randomization pointed to causal links between pain and psychiatric disorders, substance use disorders and C-reactive protein levels.[6]

343

independent genetic loci linked to multidimensional pain, 92 of them new

SOURCE 6

WHY IT MATTERS

It hands pain researchers a long list of candidates, including 490 genes prioritized through brain- and blood-specific regulation.[6]

CAVEAT *European-ancestry samples only; a version of this study was posted as a medRxiv preprint on 5 March 2025.*[6,7]

[6] doi:10.1038/s41593-026-02455-1 · [7] doi:10.1101/2025.02.28.25323112

WORDS THIS WEEK

Blood-brain barrier
The tightly sealed lining of the brain's blood vessels, which controls which molecules pass from the blood into brain tissue.

Antisense oligonucleotide
A short, chemically stabilized strand of nucleic acid that pairs with a chosen RNA to block it or to change how it is spliced.

Nociceptor
A sensory neuron that responds to potentially harmful stimuli, such as heat, irritant chemicals or tissue damage, and sets off pain and protective reflexes.

Genome-wide association
A study that scans DNA variants across the whole genome in many people to find spots that are statistically linked with a trait.

Cryptic splicing
Splicing that uses hidden sites in an RNA, slipping in or cutting out the wrong pieces; it often yields a message the cell destroys or a broken protein.

Mendelian randomization
A method that treats inherited gene variants as a natural experiment to test whether one trait plausibly causes another; it rests on strong assumptions.

SOURCES

1. PAPER H. Zhou et al., "The blood-brain barrier imports diverse neuroprotective proteins through pathways impaired early in Alzheimer's disease models," Cell (11 Nov 2026). doi:10.1016/j.cell.2026.10.039
2. RELEASE "Study rewrites the rules of the blood-brain barrier," Gladstone Institutes news release via EurekAlert! (11 Nov 2026). https://www.eurekalert.org/news-releases/1150721
3. PAPER S. S. Mali et al., "A coronavirus protease activates sensory neurons via TRPA1 to drive sneeze, cough, and pain," Neuron (12 Nov 2026). doi:10.1016/j.neuron.2026.10.017
4. PREPRINT S. S. Mali et al., "A coronavirus protease activates sensory neurons via TRPA1 to drive sneeze, cough, and pain," bioRxiv preprint (11 Jan 2024). doi:10.1101/2024.01.10.575114
5. PAPER M. J. Keuss et al., "UNC13A splice correction rescues synaptic dysfunction induced by TDP-43 loss," Nature (11 Nov 2026). doi:10.1038/s41586-026-11256-2
6. PAPER S. Toikumo et al., "Gene discovery and pleiotropic architecture of multidimensional pain in a genome-wide association study of >1.2 million individuals," Nature Neuroscience (12 Nov 2026). doi:10.1038/s41593-026-02455-1
7. PREPRINT S. Toikumo et al., "Gene discovery and pleiotropic architecture of chronic pain in a genome-wide association study of >1.2 million individuals," medRxiv preprint (5 Mar 2025). doi:10.1101/2025.02.28.25323112

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