**SYNTROPIC MEDCAL**
**Science Brief**

# Reopening the Brain's Window of Plasticity

How flickering light triggers the brain's own immune cells to dismantle the molecular brakes on learning and recovery.

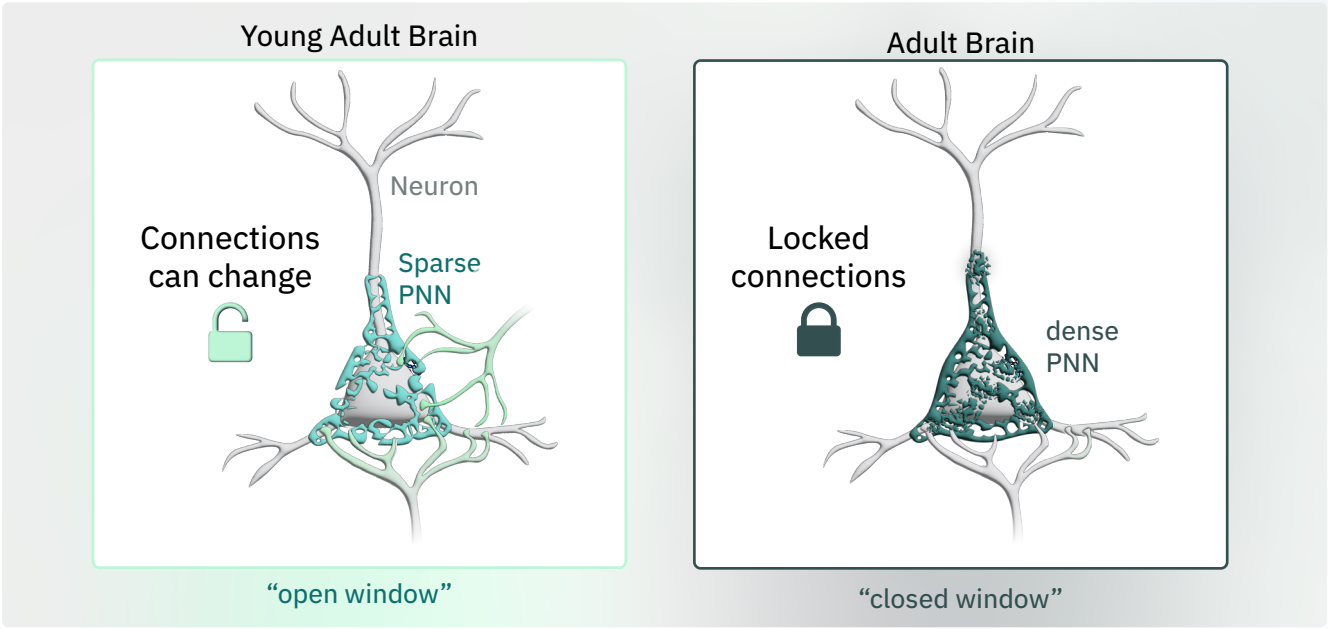
Based on: Venturino et al., Cell Reports, 2021

Section 01

## The Problem: *The cost of an experienced brain.*

Think about how easily children learn a new language or recover from a brain injury. This remarkable flexibility is known as **'plasticity'** and does not disappear in adulthood; however, it is actively suppressed. The brain deliberately trades the almost effortless learning of childhood for the stability and reliability of an adult mind with experience. In early life, this flexibility exists within so-called 'critical periods', which are temporary windows of heightened plasticity when the brain is especially receptive to change. These critical periods progressively close as adulthood approaches, stabilising the brain's connections (see **figure 1**).
One of the key molecular mechanisms behind this suppression are the **perineuronal nets (PNNs)**. PNNs are dense scaffolding structures made of a dense, mesh-like material and that wrap around specific neurons in the brain. Once established in young adulthood, they act as physical and chemical barriers, protecting the connections that neurons can form and effectively locking brain circuits into their current configuration.
Consequently, while the adult brain is highly capable, it has a limited capacity for the kind of deep, circuit-level rewiring that underlies recovery from trauma, depression or cognitive rehabilitation.

**Figure 1)** *How the brain opens and closes its window of plasticity*




The main point
To unlock these possibilities, scientists seek ways to selectively dismantle the PNN and to do so safely.

Section 02

## The Discovery: *How the Brain's immune cells get activated to remove the PNN.*

*In a 2021 study published in Cell Reports, Syntropics Co-founder Dr. Alessandro Venturino and his colleagues identified a previously unknown mechanism by which the brain can naturally remodel its own PNNs. Crucially, they also demonstrated that this mechanism can be activated from outside the brain, without the use of drugs.*

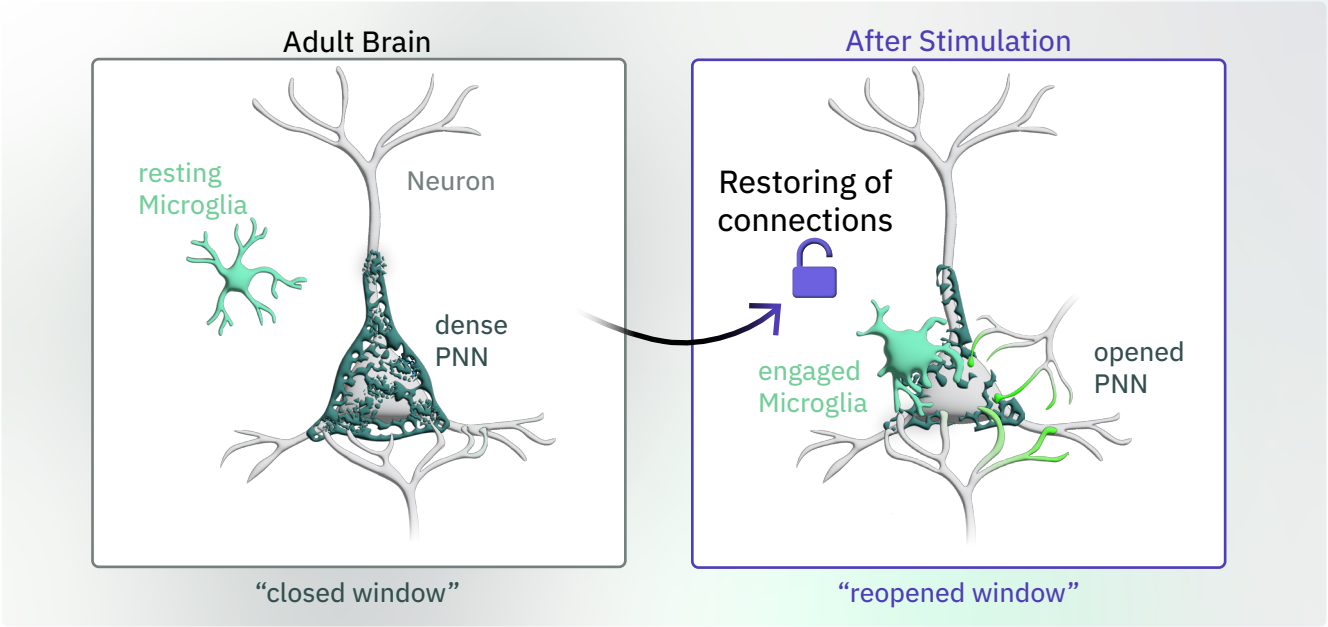
### What the researchers found

The study began with an key observation in mice: repeated exposure to ketamine caused a dramatic reduction in PNN density across multiple brain regions. Neurons that had been tightly encased in their molecular scaffolding became accessible again, and the brain regained a form of plasticity normally only seen in younger brains.

The critical discoveries were identifying the mechanism and the cells responsible. The scientists identified **microglia (the brain's resident immune cells, best known for fighting infection)** as the key agents of PNN removal. Under ketamine exposure, the researchers observed that the microglia physically moved towards PNN-coated neurons, made contact with them, and began dismantling and engulfing the PNN material. Chemical markers confirmed that this was an active, coordinated process rather than passive decay.

When the scientists pharmacologically depleted the microglia before administering ketamine, the PNNs remained completely intact. This confirmed that microglia are not bystanders, but rather the key players in this mechanism.

**Figure 2)** *Microglia reshape the PNN and "reopen the window" of plasticity*




**Key Insight**

Microglia are not simply the brain's immune defence. They are active sculptors of neural architecture and can be directed to remodel the very structures that restrict adult plasticity.

Section 03

## The Breakthrough: *Flickering light alone can promote PNN removal and neuroplasticity.*

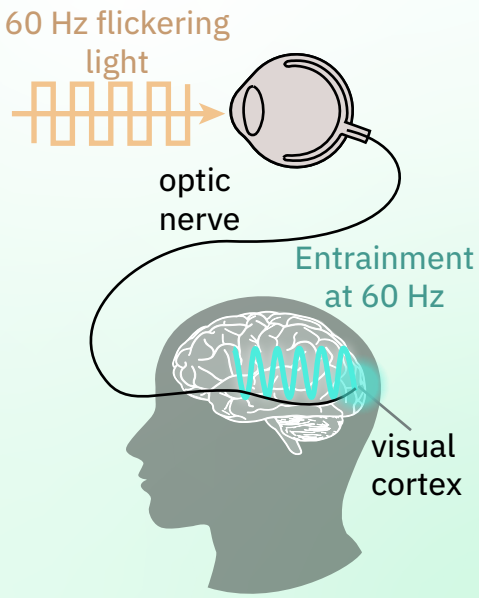
Although ketamine has important uses, such as in the treatment of treatment-resistant depression (TRD), repeated doses are not a practical therapeutic strategy for all patients. **The researchers therefore asked: what is the underlying signal that recruits microglia to PNNs?**

The answer lies in brain rhythmic oscillations. Ketamine is known to alter neural oscillations in the gamma frequency range (roughly 30–80 Hz). Gamma oscillations are produced by the very neurons wrapped in PNNs (fast-spiking parvalbumin-positive interneurons), and microglia are sensitive to the chemical signals released by neurons during activity. The researchers therefore used a process called **entrainment** (see box) to ask whether flickering light at specific frequencies, delivered non-invasively to awake and freely moving mice, could drive the same microglia response.

### What is *entrainment*?

Neurons across the brain fire in coordinated rhythmic bursts. These rhythms, called oscillations, occur at characteristic frequencies measured in Hertz (Hz, or cycles per second). **Entrainment** is the process of driving the brain into synchrony with an external rhythmic stimulus. When a light flickers at a precise frequency, neurons in the visual cortex begin to fire in time with it, and this rhythm can spread to wider networks.

The study by Dr. Venturino and colleagues showed that entraining the brain at 60 Hz (but not at other tested frequencies) was sufficient to activate microglia and trigger PNN remodelling. This reveals that microglia are tuned to respond selectively to specific patterns of neural activity.




**The results were striking.** 5 days of daily 2 hour exposure to 60 Hz flickering light reproduced key hallmarks of ketamine-induced PNN remodelling in healthy adult mice:

- Significant reduction in PNN-coated neurons in the visual cortex,
- Microglia moving closer to parvalbumin-positive neurons,
- Elevated levels of MMP-9, an enzyme involved in PNN breakdown, in both neurons and microglia,
- PNN fragments detected inside microglial compartments, confirming active engulfment.

Critically, this effect was highly frequency specific. Light flickering at 8 Hz (theta) or 40 Hz, and constant light, did not affect PNNs under these conditions. When microglia were depleted before 60 Hz stimulation, the effect disappeared entirely, confirming that light does not act on PNNs directly, but exclusively through microglial activation.

Section 04

## What this means for Syntropic: *Therapeutic implications.*

The Venturino et al. findings establish the biological foundation for a new class of therapeutic intervention; using precisely calibrated light stimulation to direct the brain's own microglia toward targeted remodelling of the PNN.

**The implications span several areas in medicine:**

- **Treatment for depression**: Restoring circuit-level plasticity may allow patients to form new patterns of thought and response that classical drug treatment alone cannot reach.
- **PTSD and trauma disorders**: Fear memories are encoded in highly stable circuits. Reopening plasticity provides a biological window during which behavioural therapy may achieve deeper and more lasting rewiring.
- **Cognitive rehabilitation**: Following stroke or injury, the window for recovery is narrow. Non-invasive tools that re-engage plasticity mechanisms could extend and enhance rehabilitation.
- **Neurodegenerative disease:** The same microglial mechanisms active at 60 Hz overlap with those involved in brain maintenance more broadly. Understanding frequency-specific microglial behaviour opens avenues for early intervention.

**Ongoing Clinical Trials & Next Steps**

Syntropic's research programme is actively advancing, with two clinical trials completed and two additional studies currently ongoing or in the planning phase. Our work focuses on extending stimulation protocols to clinical populations, further investigating the underlying biological mechanisms, and developing an optimised device form factor for real-world therapeutic use.

For the latest updates on trials and publications:

**syntropicmedical.com**

Section 05

## From mechanism discovery to a treatment: *Further information.*

The Venturino et al. study established the biological proof of concept in mice. Syntropic's mission is to build the bridge from that discovery to a safe, effective, and scalable human therapy. Below is a summary of where that science stands today, and where to read further.

### Additional Readings

**Microglia enable mature perineuronal nets disassembly upon anesthetic ketamine exposure or 60-Hz light entrainment in the healthy brain**

Venturino A, Schulz R, De Jesus-Cortes H, Maes ME et al., The study that started it all, first mechanistic evidence for 60 Hz microglia-mediated PNN remodeling.

pmc.ncbi.nlm.nih.gov/articles/PMC8284881/ Cell Reports 2021

**Exploring neural entrainment and synchrony in response to repeated 60 Hz flickering white light in healthy volunteers**

Alamalhoda MA, Leesch F, Giovanetti F, Dunne E, Pilloni G, Caffrey M, O'Keeffe J, Venturino A, Ferretti MT. First demonstration of robust 60 Hz cortical entrainment in humans, and progressive reduction in entrainment strength over 3 weeks of daily stimulation.

journals.plos.org/plosone/article?id=10.1371/journal.pone.0332310 Plos ONE 2025

**When Light Leaves the Lab: A Breakthrough for Depression Treatment**

Giovanetti F, Venturino A. 2025

www.inspirethemind.org/post/when-light-leaves-the-lab-a-breakthrough-for-depression-treatment

**From Olympics to neuroplasticity**

Ferretti MT. 2025

www.linkedin.com/pulse/from-olympics-neuroplasticity-maria-teresa-ferretti-6zpqf/?trackingId=Zj5jxm68S7%2Bx3pGqeKN3Pw%3D%3D

**Authors**

Ferretti MT provided input on the structure, conceptual framework, and content. Leesch F led the drafting and writing of this Science Brief. Venturino A and the Syntropic Medical team contributed to reviewing and refining the document.

**AI Assistance Disclosure**

This Science Brief was developed with the assistance of Claude Sonnet 4.6 (Anthropic), which was used for brainstorming content structure, drafting and refining text, and generating design suggestions. All scientific content was reviewed, verified, and approved by the Syntropic Medical scientific team. The conclusions and interpretations presented are those of the authors and reflect the peer-reviewed literature cited herein ( based on Venturino et al., 2021).