

Neurobiology

Wake up microglia! How brain state regulates immune cells

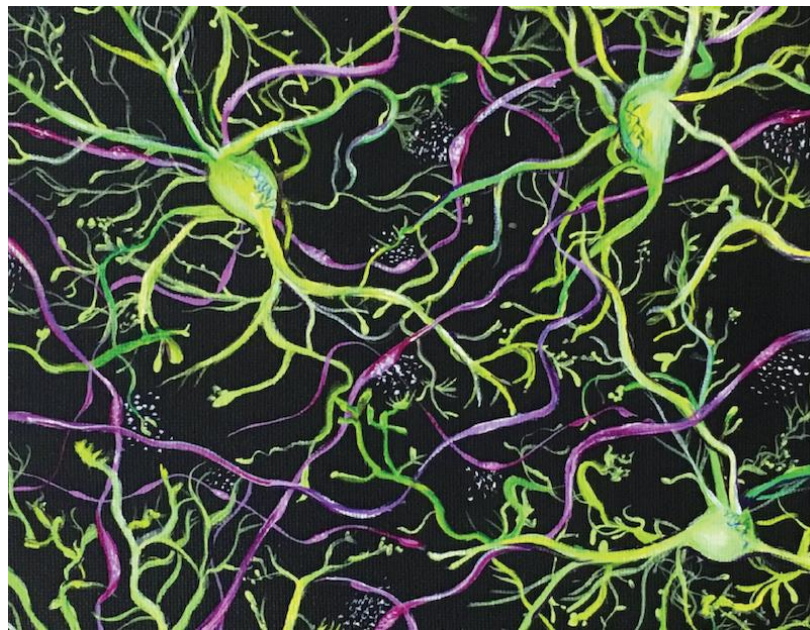
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ABSTRACT

Microglia, the immune cells of the brain, helps the brain modify its circuits in response to new experiences. In a recent study, we found that microglia helping to rewire the brain may be dependent on whether the organism is awake or asleep.



Artistic rendering of images collected by microscopy shows microglia (green) surrounded by neuronal axons (magenta) releasing norepinephrine (white speckles) in the waking brain.

Image credits: Rianne Stowell

Historically, [neuroscience](#) focused on neurons, the functional cellular units of communication in the brain. However, exciting recent advances in microscopy have revealed the importance of many other cell types in essential brain functions. Amongst these supporting players in the brain are [microglia](#), the immune cells of the brain.

Initially, neuroscientists thought that microglia, as immune cells, only act in cases of injury, disease, or infection. However, we now know that microglia play many important roles in brain development and plasticity over the lifespan. [Plasticity](#) is the process by which the brain incorporates new experiences

into existing neuron connections, in part through physical changes in the connections between neurons. Recently, microglial roles in plasticity have become a focus of research which revealed that microglia interact with neurons to facilitate these physical changes. Following up on this previous work, our study indicated that awake brains inhibit microglial roles in response to brain injury and plasticity.

Neuroscientists long assumed that microglia remain static in the absence of injury or infection. However, the new techniques that allowed visualization of these cells in the living brain revealed that microglia

are instead remarkably dynamic. The many branches protruding from each microglial cell body move rapidly through the local brain environment, constantly reaching out and interacting with different components of their surroundings and mediating plasticity. The discovery of microglial dynamics and their participation in plasticity were exciting and raised many questions about how microglia function in the normal healthy brain. Prior to our study, researchers imaged microglia mostly in animals that were anesthetized, meaning a sleep-like state. Instead, we wanted to explore microglia in awake animals and determine whether differences in microglial behavior could influence plasticity.

To study microglia in awake mice, we used a specific type of microscopy which allows us to visualize microglia inside living tissues. Using this technique we, and others in the field of neuroscience, can monitor cell behavior over extended periods. In our study, we imaged the same mice with awake and sleep-like brain states which enabled us to compare how the same brains behave in these two states.

In the sleep-like state, we found that microglial branches spread out and allow microglia to occupy and interact with more of the brain environment whereas such microglial dynamics are greatly reduced in awake brains. We were able to determine the increased concentrations of [norepinephrine](#) (a type of adrenaline which transmits signals in the brain) in the awake brain cause microglia to retract their branches and survey less of the brain

environment. Importantly, we found that microglia are slower in responding to a brain injury when animals are awake. Additionally, simulating a continuously awake state inhibited plasticity in mice.

Our findings indicate that, in sleep-like states, microglia can better monitor their environment, respond to injuries, and participate in plasticity. These discoveries suggest that if microglia receive prolonged awake signals, they will be less able to help the brain respond to environmental signals that drive both normal brain function and pathological changes. Our study is the first to show that microglia respond to changes in brain state and norepinephrine is the key signal to microglia that the brain is awake.

We concluded that the brain state guides how microglia behave and interact with neurons. These findings highlight the importance of healthy sleep-wake cycles as extended wakefulness can prevent normal microglial interactions with neurons and responses to injury. Recognizing how brain state influences microglia will help research on diseases related to altered sleep and awake states, which include neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. Future work can investigate how sleep (rather than anesthetic/sleep-like state) impacts microglia in the brain and what other signals may ultimately regulate their roles in brain health and disease.