Tracing maternal behavior to brain immune function

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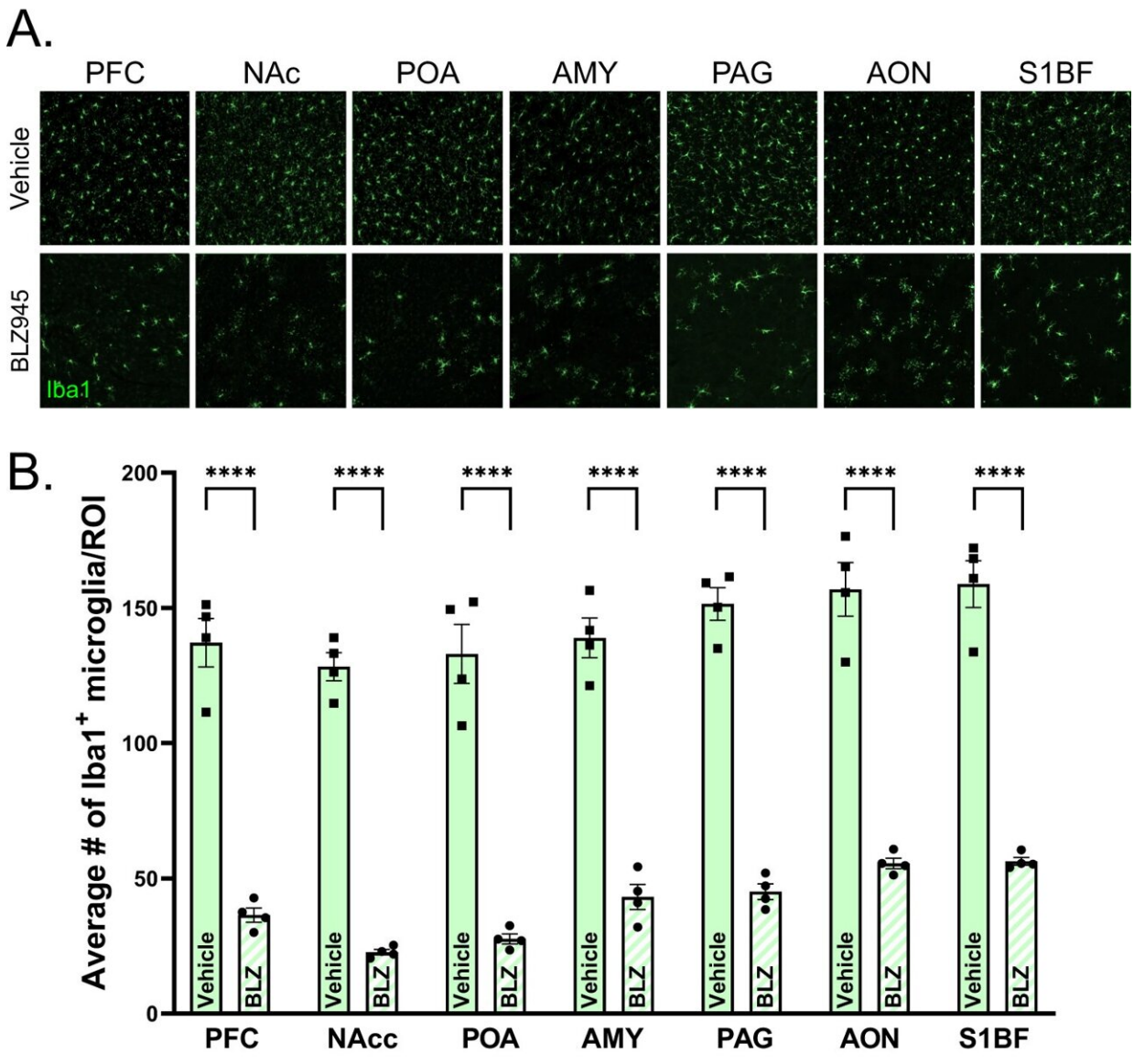

BLZ945 treatment led to rapid depletion of microglia in the adult female rat

brain. Credit: *Neuropsychopharmacology* (2023). DOI: 10.1038/s41386-023-01624-1

Immune system changes in the pregnant body that protect the fetus appear to extend to the brain, where a decrease in immune cells late in gestation may factor into the onset of maternal behavior, new research in rats suggests.

In adult female rats that had never given birth—which typically don't like being around babies—depletion of these cells sped up their care for rat newborns that were placed in their cage.

The loss of these cells, called microglia, and the related uptick in motherly attentiveness were also associated with changes to neuron activity in several regions of the rat brain, suggesting shifts in immune function have a role in regulating maternal behavior.

Microglia are well-known for their link to brain injury and disease because of their protective activities under those circumstances, and for helping enable brain development. But these findings suggest they have another job entirely in the adult brain.

"Our data shows that microglia are probably also really important for plasticity in the adult brain—its ability to adapt to all kinds of changes—and contribute to normal behavioral function," said co-senior author Kathryn Lenz, associate professor of psychology at The Ohio State University.

The findings also suggest that feeling maternal is much more than just a hormonal response.

"The standard way of thinking up to now about mothers is that hormones are the primary drivers of maternal care. But this really draws attention to the importance of immune changes to maternal behavior," said co-senior author Benedetta Leuner, associate professor of psychology at Ohio State. "These data are novel and potentially paradigm-shifting."

The research was published recently in the journal *Neuropsychopharmacology*.

Lenz and Leuner reported in previous work in rats that microglia in the brain decrease late in pregnancy. In this study, they set out to figure out why.

"More is known about how the immune system changes to support a healthy pregnancy. One of the key functions is a shift in the immune system in order to tolerate the fetus, which is a non-self entity," Lenz said. "But honestly, very little is known about what's happening in the brain's immune system during and after pregnancy."

Though rats that haven't given birth tend to dislike babies, they can be gradually coaxed into caring for rat pups through a process of repeated exposure. For this study, the researchers tested whether loss of microglia would make a difference in how non-mother rats behaved toward foster pups.

The team gave non-mother female rats either two doses of a drug that depletes microglia or, for control animals, a sham substance that doesn't affect cells. Once microglia levels had decreased by about 75%, pups were placed in the non-mothers' cages, and researchers monitored the adult rats' behavior toward the newborns. Results showed that compared to controls, the rats with depleted microglia were fully sensitized to maternal behavior significantly faster.

"This manipulation of microglial depletion—making the immune environment of the non-mother brain look like the immune environment of the maternal brain—led to behaviors that were different from the non-treated animals," Leuner said. "And even on the days before they met the criteria for displaying maternal behavior, they started approaching the pups and were sniffing and licking them more."

Researchers then screened the rats' brains for a protein marker of where neuron activation had increased or decreased over time. Overall, the patterns of activation were significantly different between controls and rats with depleted microglia.

A few affected brain regions in rats with depleted microglia stood out for their potential connection to maternal behavior: Increased neural activity was found in the prefrontal cortex, important for executive functioning—being able to meet goals, stay focused and display self-control—and decreased neural activity was evident in two regions that are part of aversion circuits.

Though the accelerated onset of maternal behavior was clearly linked to microglia depletion, there is still more to learn about that mechanism, as well as the changes in neural activity patterns—did the loss of microglia drive widespread alterations to neuronal activation, or did neurons in specific brain regions respond to the rats' uncharacteristic behavior changes?

And finally, do microglia functions differ according to sex? Up until fairly recently, most microglia studies were done in male animals—so finding this connection between prominent immune cells and female reproduction opens the door to a whole new area of investigation.

"Learning about microglia function in the life history of a female adds real complexity to our understanding of what these cells do," Lenz said.

"That's incredibly important."

More information: Courtney N. Dye et al, Microglia depletion facilitates the display of maternal behavior and alters activation of the maternal brain network in nulliparous female rats, *Neuropsychopharmacology* (2023). DOI: 10.1038/s41386-023-01624-1

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