NEWS

Brain imaging study points to microglia as autism biomarker

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Rainbow bright: The brain of an individual with autism (bottom) shows more activated microglia than a control brain does (top).

Microglia, brain cells that are part of the immune system, are more activated in young men with autism than in controls, according to a brain imaging study published 26 November in the *Archives of General Psychiatry*[1].

Postmortem studies have shown that **microglia are altered in autism**, but the new study marks the first time that researchers have tracked the cells in living people with the disorder.

Microglia are known to rapidly transform from a spider-shaped resting state into a bulbous active state when they're fighting off infection or damage. But the role of activated microglia in autism and related disorders is complex and largely mysterious. For example, studies in the past couple of years have shown that active microglia are important not only for immunity, but for the **development of a healthy brain**.

It's not yet clear what the findings from the new study mean. But experts say that tracking microglia activity in live brains could be used as a **biomarker** of how the brain changes over time, such as before and after a new treatment.

“Doing this *in vivo* characterization gives a more dynamic perspective of what these cells are doing in the brain,” notes **Carlos Pardo**, associate professor of neurology and neuropathology at Johns Hopkins University in Baltimore, who was not involved in the work.

In the new study, researchers from Japan used a type of brain scanning called positron emission tomography (PET) to track the distribution of microglia in the brain. Their scans point to an abundance of activated microglia in men with autism, particularly in the cerebellum — a region known to process sensory information, movement and learning, and which has also been **linked to autism**.

The data echo what’s been seen in postmortem tissue. For example, in a landmark study in 2005, Pardo’s team showed that cerebellar tissue from individuals with autism shows an excess of activated microglia and contains certain chemicals, called cytokines, that are involved in inflammatory responses[2].

Tricky tracer:

In PET scanning, radioactive tracers injected into participants’ blood make their way into the brain, bind to specific receptors, and can then be seen with a brain scanner.

In this case, the researchers used a tracer dubbed [11C](R)-PK11195, which binds to activated microglia. The tracer has been used for decades in people with various neurological disorders. It had not been used in people with autism, however, because the link between microglia and the disorder is relatively new.

The researchers injected the tracer into 20 men with high-functioning autism and 20 controls matched by sex, age and intelligence quotient. They found that the tracer binds more strongly in the brains of the participants with autism, presumably because they have more activated microglia.

This was true across all brain regions tested, says lead investigator **Kazuhiko Nakamura**, associate professor of psychiatry and neurology at Hamamatsu University School of Medicine in Shizuoka, Japan. “But the most prominent increase was evident in the cerebellum.”

No one knows what activated microglia may be doing in the brains of people with autism, some experts note. Others are concerned by some of the details of the study’s design.

For example, the tracer isn’t specific to activated microglia. It can also bind other brain cells, including astrocytes, star-shaped cells whose long projections **help support synapses**, the junctions between neurons.

Less frequently, the tracer also binds resting microglia and neurons, notes **Robert Innis**, chief of the molecular imaging branch of the National Institute of Mental Health, who was not involved in

the new study.

Innis is using tracers that are more specific to activated microglia in people with autism. Nakamura says his team, too, is developing more specific tracers.

The new study's design is also not ideal, according to Innis, because the researchers didn't simultaneously look at the tracer in both the blood and brain. This comparison can rule out the possibility that people with autism simply process the tracer differently.

"Maybe the patients are just not metabolizing this drug as fast, and therefore more of it is getting into the brain," Innis says.

Nakamura agrees that this is a possibility, but argues that metabolic abnormalities are unlikely because the scans indicated that there were no differences in blood flow in the brains of people with autism and controls.

Because it requires exposure to radiation, PET scanning is usually not done on children, especially for studies that require a healthy control group.

But newer microglia markers that require less radiation than conventional markers could conceivably be used to track the effectiveness of a therapy. "I could see it being extended into research studies of anti-inflammatory therapies, where the child acts as their own control," Innis says.

Methodological issues aside, other researchers question the meaning of the data. Several big questions remain unanswered, such as whether activated microglia are a cause or consequence of autism, notes **Jonathan Kipnis**, professor of neuroscience at the University of Virginia in Charlottesville.

Last year, Kipnis' team reported that **replacing the microglia** in mice that model Rett syndrome alleviates some symptoms and extends the mice's lives. Intriguingly, these mutant animals seem to have under-active microglia, he says, illustrating that the cells' role in neurodevelopmental disorders is not straightforward.

"Just looking at the number of microglia, and whether they're activated or not — I'm not saying it's meaningless," Kipnis says, "but it's not meaningful enough."

REFERENCES:

1. Suzuki K. *et al. JAMA Psychiatry* Epub ahead of print (2012) **Abstract**
2. Vargas D.L. *et al. Ann. Neurol*. **57**, 67-81 (2005) **PubMed**