In NFL Players, Brain Inflammation May Persist Years After Head Trauma

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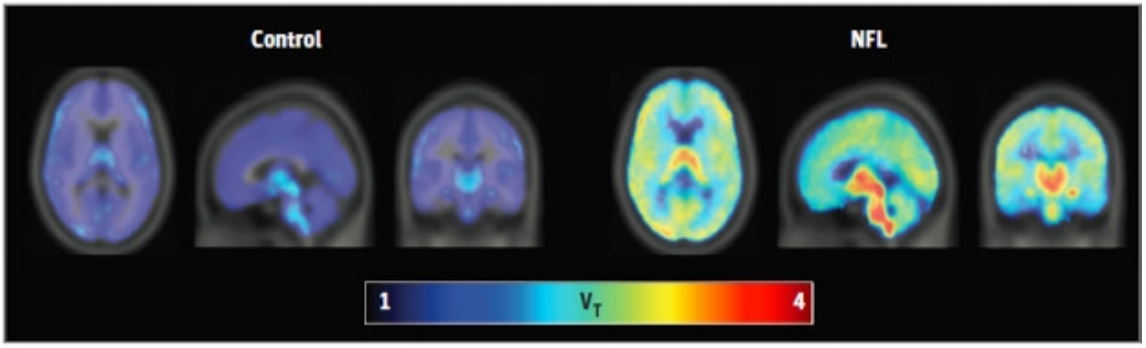
Research has shown that sports-related head injuries lead to future amyloid and tau pathology, as well as a higher risk of dementia and neuropsychiatric symptoms. However, the link between traumatic brain injury (TBI) and these ensuing problems is unclear. Could inflammation play a role? Scientists led by Martin Pomper, Johns Hopkins Medical Institutions, Baltimore, report online in the November 28 JAMA Neurology that NFL players' brains are replete with activated glial cells even without obvious neuropsychiatric problems. This finding suggests that neuroinflammation could be a marker for problems down the road.

"Overall, this study adds to the accumulating evidence that microglia activation is an early response to the repetitive head trauma that occurs during football play," wrote Ann McKee, Boston University, to Alzforum.



Concussive Impact. *NFL players (right) bind more TSPO ligand than matched controls (left), suggesting glial cells are activated. [Courtesy of JAMA Neurology, © 2016 American Medical Association. All rights reserved.]*

Prior PET imaging studies with a ligand that binds a microglial transporter protein, called TSPO, suggest that these cells kick into high gear in people who sustain a single severe blow to the head, and that this may be associated with cognitive impairment (Ramlackhansingh et al., 2011). Researchers theorize that after brain injury, chronic inflammation contributes to cellular and structural damage, leading to depression and cognitive decline (Witcher et al., 2015). However, few reports have examined whether this plays out in the brains of athletes who experience repeated mild concussions. Previously, McKee and colleagues reported an abundance of activated microglia in deceased football players compared with controls (Cherry et al., 2016).

This occurred most prominently in old athletes decades after retirement, but cropped up even in young players. Using PET, Pomper and colleagues found evidence for microglial activation in older former NFL players (Coughlin et al., 2015). However, these athletes were at increased risk for inflammation due to cardiovascular disease and other problems of aging. To eliminate those confounding factors, the researchers decided to repeat the study in younger players.

To image activated glia, the authors used a PET ligand called [11C]DAP-713. This agent also binds to TSPO, but with greater specificity than some of the early TSPO PET ligands. First author Jennifer Coughlin and colleagues scanned the brains of 14 NFL players—four active and 10 who had retired within the last 12 years—at an average of seven years since their last concussion. One player's last concussion was 21 years prior, while another was concussed just a year before the scan. Coughlin also scanned 16 active controls matched for age, sex, education, and body mass index, and who had no history of TBI. The average ages of players and controls were 31 and 28 years, respectively. In addition, the scientists conducted neuropsychological tests, structural magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI), which measures the movement of water in brain tissue to estimate damage to white matter.

PET scans revealed that glial cells were indeed more active in these young NFL players compared to controls. Their brains lit up with DAP-713, especially in the bilateral hippocampus, parahippocampal cortex, and supramarginal gyrus, as well as the left entorhinal cortex and temporal pole (see image above). In contrast, there were no significant differences in brain volume or neuropsychological measures of learning, memory, or depression between athletes and controls. Only slight white matter changes appeared in NFL players' DTI scans, indicating damage in the right posterior thalamic radiation and left anterior corona radiata.

The data suggest that inflammation occurs in players who experience repeated head injuries, and that glial cells can remain revved up for years after injury, said Coughlin. Longitudinal studies will be required to examine whether TSPO binding predicts TBI-related complications, wrote Kristina Witcher and Jonathan Godbout of Ohio State University, Columbus, in an accompanying editorial. Since neuropsychiatric complications and neurodegenerative diseases appear much later, such a finding could open a window of opportunity for preventative anti-inflammatory treatment, they wrote.

Anna-Leena Sirén, University of Würzburg, Germany, pointed out that brain areas relevant for cognitive function seemed to strongly take up the PET ligand in this study (see full comment below). Chronic neuroinflammation after sport-related injuries may drive neurodegeneration there, since activated microglia can be involved in synaptic remodeling and contribute to the spread of tau pathology, she noted (Vasek et al., 2016; Maphis et al., 2015).

Researchers are still unsure what TSPO activation means physiologically, since the ligand does not distinguish between different forms of activated microglia. Scientists believe some of these cells are harmful, spewing out inflammatory chemicals, while others may protect by devouring debris caused by injury. Whichever DAP-713 labels, it is clear the signal marks spots of neuronal injury and repair, said Coughlin. DAP-713 may also pinpoint glia that are primed to turn

inflammatory after a second insult, such as another brain injury, as has been reported in animals (Rowe et al., 2016). TSPO also cannot distinguish between activated microglia and reactive astrocytes. McKee noted that her recent postmortem study found the former, not the latter, in deceased football players

Coughlin and colleagues aim to expand this study by imaging more players and controls over time, while measuring fluid biomarkers as well. This may reveal how inflammation ties in with neuropsychiatric symptoms. “We need to better understand the [innate] immune response to inform therapeutic strategies, such as which anti-inflammatory drugs might help these players,” she said. More research is also needed before TSPO-PET becomes a routine part of post-concussion monitoring or care management, she said.—Gwyneth Dickey Zakaib

COMMENTS

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Comments on this content

Anna-Leena Sirén

Posted: 02 Dec 2016

How chronic traumatic brain injury leads to dementia and increases the risk for neurodegenerative disease is not known. This study by Coughlin et al. provides evidence for the role of chronic inflammation, perhaps already early in these processes, by demonstrating profound chronic activation of microglia after mild sport-related head injuries in young football players. As stated in the accompanying commentary, increased TSPO expression might not be direct proof of a chronic proinflammatory state of microglia, but there are robust experimental data showing increased binding of TSPO ligands in activated proinflammatory microglia and a sustained microgliosis in rodent models of brain trauma.

Importantly, Coughlin et al. report that brain areas relevant for cognitive function seemed to be strongly affected. Since activated microglia can be involved in synaptic remodeling (Vasek et al., 2016) contribute to spreading of tau pathology (Maphis et al., 2015), the chronic neuroinflammatory response after sport-related injuries may be the driver of neurodegeneration. As new noninvasive PET-imaging ligands for monitoring of tau pathology become available (Barrio et al., 2015), it would be interesting to further examine tau pathology and microglia activation in the course of mild sport-related head injuries.

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