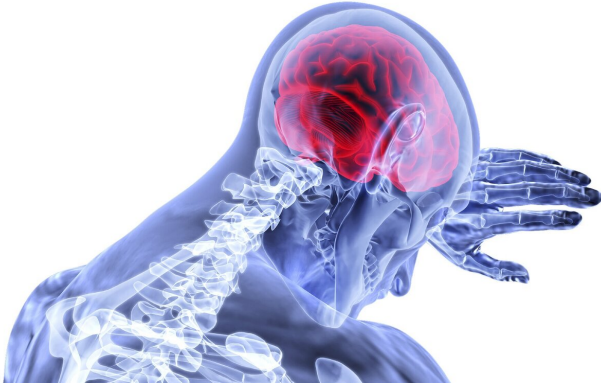# McKee CTE staging scheme accurate in diagnosing severity, location of disease

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Since 2008, researchers at Boston University School of Medicine (BUSM) and VA Boston Healthcare System have studied Chronic Traumatic Encephalopathy (CTE), a progressive brain disease associated with repetitive head impacts that has been diagnosed after death in the brains of American football players and other contact sport athletes as well as members of the armed services.

In 2013, these same researchers proposed criteria for the pathological diagnosis of CTE and a methodology for grading the severity of the disease known as the McKee CTE staging scheme. The McKee staging scheme defined four pathological stages of CTE, stages I (mild) to IV (severe), based on the density and regional deposition of hyperphosphorylated tau (p-tau) pathology. The criteria for pathological diagnosis of CTE were adopted and refined by the National Institute of Neurological Disorders and Stroke/National Institute of Biomedical Imaging and Bioengineering consensus panel of expert neuropathologists in 2015. Since then, although the staging scheme has been used widely to characterize the severity of pathology in hundreds

of CTE subjects, its effectiveness and accuracy has not been formally tested.

Now a new study for the first time proves that the McKee staging scheme for CTE accurately represents the progression of tau pathology in CTE and correlates with clinical dementia. It also confirms that it correlates with age at death and years of American football play.

To test its effectiveness and accuracy and provide a detailed examination of the regional distribution of p-tau in CTE, researchers from Boston University examined the relationship between the McKee staging scheme and p-tau pathology in regions throughout the brain, age at death, dementia and years of American football play among 366 male brain donors neuropathologically diagnosed with CTE. They found having a higher CTE stage was associated with higher scores on all assessments of p-tau severity and density and ultimately more clinically advanced CTE. Severity and distribution of p-tau in CTE followed an age-dependent progression, meaning older age was associated with increased odds for having a higher CTE stage and CTE stage was independently associated with increased odds for dementia.

In addition, the researchers identified five areas in the brain where there were clusters of increasing p-tau pathology that conformed to CTE stage, age at death, dementia and years of American football play. Tau pathology was consistently most severe in five brain regions: dorsolateral frontal cortex, superior temporal cortex, entorhinal cortex, amygdala and locus coeruleus. In the youngest brain donors with the least advanced CTE stage, tau pathology was most severe in dorsolateral frontal cortex and locus coeruleus.

"These findings further advance our understanding of CTE and lay the groundwork for diagnosis during life using brain imaging techniques that can identify the specific tau of CTE in the brains of living

people. This work will also help focus the development of therapies aimed at arresting tau progression," explained corresponding author Ann McKee, MD, chief of neuropathology at VA Boston Healthcare System and director of the BU CTE Center.

While further study is needed to clarify the clinical correlates of CTE across the different stages of disease and identify repetitive head impacts (RHI) and non-RHI related risk factors that enhance susceptibility and course progression, these findings support the usefulness of the McKee CTE staging scheme in assessing CTE pathological severity and support their continued use in the study of CTE.

"This study addresses a key knowledge gap in the field by confirming the usefulness of the McKee CTE staging scheme and directly linking the tau from CTE with age, years of American football play and dementia. The findings will play an important role in guiding both clinical and basic science research on CTE," said lead author Michael Alosco, Ph.D., associate professor of neurology at BUSM and co-director of the BU Alzheimer's Disease Center Clinical Core.

These findings appear online in the journal *Acta Neuropathologica*.

Provided by Boston University School of Medicine
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