Diagnosing CTE in Living Patients with PET/MRI and AI

Introduction to Neuroscience 2026, Tristan Lee

1. Introduction

CTE, short for Chronic Traumatic Encephalopathy, is a brain disease linked to repeated hits to the head. This disease shows up in people who played contact sports for years, in boxers, in soldiers exposed to blasts, and in others who took many blows to the head over time. Here is the strange part: right now, doctors cannot diagnose CTE while a person is alive. The only way to confirm CTE is to examine the brain after death, under a microscope.

This single fact causes many problems. A doctor who sees a retired football player struggling with mood swings, memory loss, or trouble controlling impulses can suspect CTE, but cannot prove CTE while the person remains around to get help. Drug companies cannot test new treatments either, because no method exists to confirm which living patients actually carry the disease. Families are left without answers, and the athletes themselves live with uncertainty, a real concern given how much attention CTE receives in football and other contact sports right now.

Because no direct test exists, doctors currently use a related label called TES, which stands for Traumatic Encephalopathy Syndrome. TES is not a CTE diagnosis. TES functions as an educated guess, built from a person's history of head injuries and that person's symptoms. Scientists are trying to build a real, direct test for CTE in living people, and this paper looks at how far that effort has come.

2. Background: What Is CTE, and Why Is It Hard to Detect?

CTE damage comes from a protein called tau. Tau normally helps hold the internal structure of brain cells together. After repeated head impacts, tau can become chemically altered (doctors call this hyperphosphorylated, meaning extra phosphate groups get stuck onto the protein), and the altered tau clumps up in ways healthy tau should not. Pathologists diagnosing CTE at autopsy look for these clumps in a very specific location: clustered around small blood vessels, deep in the folds of the brain's surface. Alzheimer's tau, by contrast, spreads more evenly across the whole surface of the brain. That difference in pattern is how examiners tell the two diseases apart after death, and this difference explains a large part of why CTE stays hard to catch with a scan, since any brain scanner must be able to detect that same pattern in a living person's skull.

A chemistry problem sits underneath that pattern too. Even though both diseases involve the same tau protein, the CTE version of tau folds into a different 3D shape than the Alzheimer's version. This shape difference matters enormously for scanning, because imaging tracers work the way specially shaped keys work, fitting only one specific lock. A tracer built to recognize the Alzheimer's shape of tau does not reliably stick to the CTE shape.

The damage also follows a pattern that matches the symptoms doctors see. Early damage starts in the front and side regions of the brain that control mood and impulse control, matching the irritability and impulsiveness families often report. As the disease worsens, damage spreads toward memory-related structures, matching the memory loss that shows up later. The wiring beneath these regions (white matter, the brain's cabling) gets damaged too, both from direct impact and as a follow-on effect once nearby brain cells start dying.

The TES framework mentioned above combines two things: a documented history of repeated head impacts, plus a pattern of symptoms that gets worse over time rather than staying the same. Researchers have also noticed that people with a history of repeated head impacts are more likely to have an enlarged cavum septum pellucidum, a small structural quirk in the middle of the brain, which can serve as another supporting clue. But TES was built as a research tool, not a proven diagnostic test, and nobody has yet checked, on a large scale, how often a TES diagnosis actually matches what is found at autopsy. That gap between the clinical guess and the biological truth is the problem the rest of this paper explores.

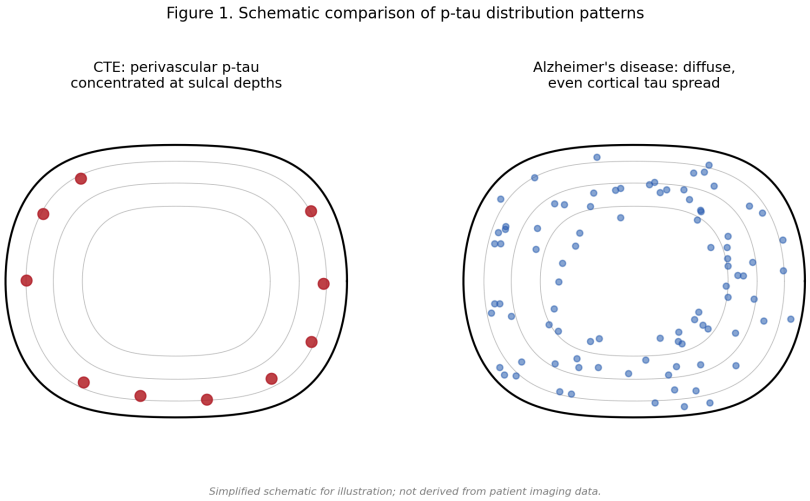

Figure 1. CTE tau concentrates in focal, perivascular deposits at the depths of cortical sulci, while Alzheimer's tau spreads more evenly across the cortical surface. This distribution difference is what pathologists rely on at autopsy, and it's also the likely reason AD-optimized PET tracers bind CTE tissue so weakly.

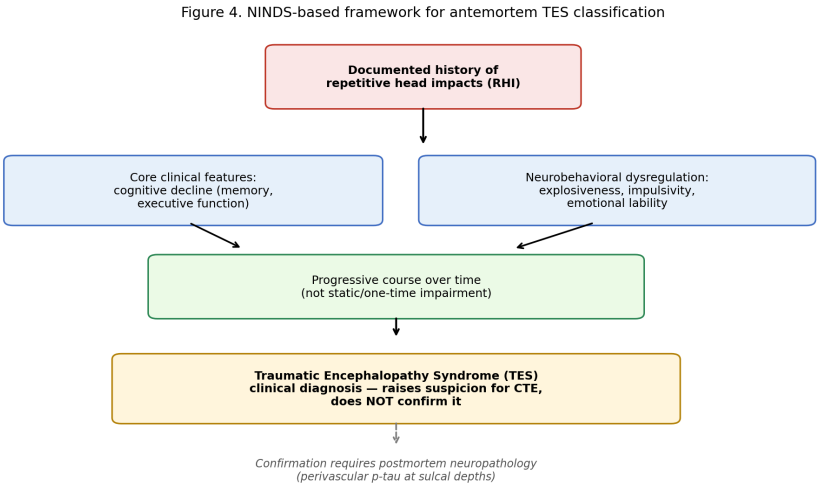

Figure 2. The TES framework combines exposure history with a core clinical profile and a progressive course. It flags who is worth investigating further, but a TES diagnosis on its own stops well short of confirming CTE.

3. What Scientists Are Trying: Four Approaches

Brain scans that light up tau (PET imaging)

PET scanning works by injecting a chemical tracer that lights up on a scanner after finding and sticking to a target, in this case, tau clumps. The first tracer approved for this kind of scanning, called flortaucipir (brand name Tauvid), was built and tested for Alzheimer's tau. When scientists pointed this same tracer at suspected CTE cases, the tracer barely worked. Binding was weak and unreliable, almost certainly because, as explained above, CTE tau carries a different shape than Alzheimer's tau.

That mismatch pushed researchers to design a tracer specifically for the CTE shape of tau. A team based at the University of Toronto and the University of Pittsburgh, working with a company called Oxiant Discovery, tested more than 150 candidate chemicals before landing on one called OXD-2314. In 2026, this team ran the first study of the new tracer in living people, comparing three retired athletes with suspected CTE to seven healthy volunteers. The suspected-CTE group showed a clearly different signal on the scan, at the boundary between gray and white matter in the brain, a pattern the research team said had not shown up with older tracers. Later checks on donated brain tissue from confirmed CTE cases, using the same chemical, found strong binding exactly where

expected. The lead scientist on the study, Isabelle Boileau, said the approach could potentially reach patients within about two years, if larger studies back up these early results.

Honesty about the size of this study matters though: three suspected-CTE patients counts as a very small number. This result stands as promising early evidence, not proof that the scan works reliably across all kinds of patients.

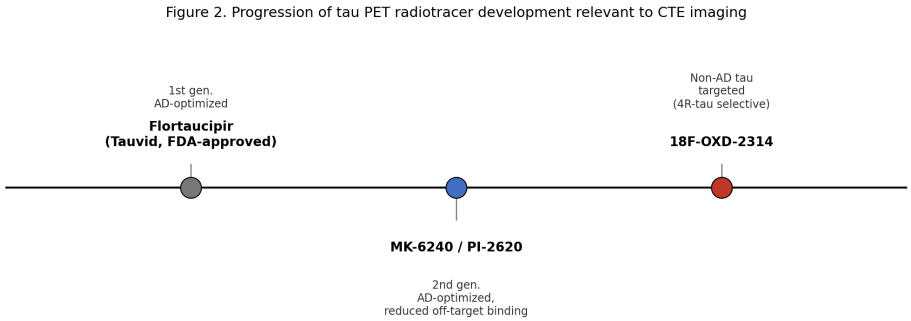

Figure 3. Tau PET tracer development has moved from AD-optimized compounds toward radiotracers purpose-built for the non-AD tau fold seen in CTE. OXD-2314 is still at the first-in-human stage, tested so far in only three suspected CTE cases.

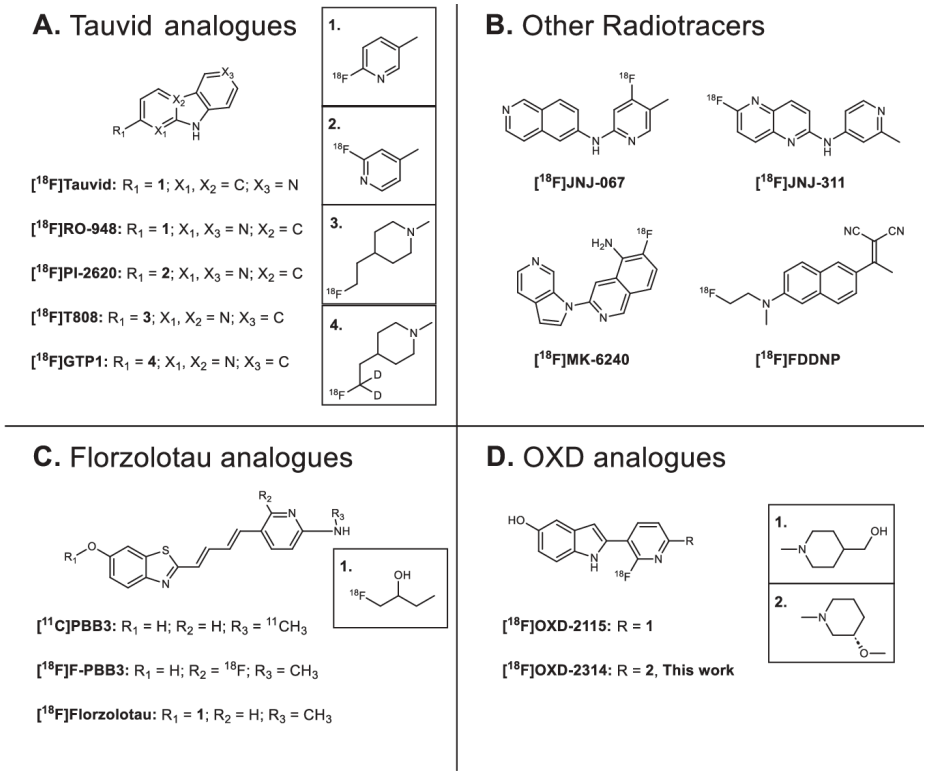

Figure 4. Chemical structures of tau PET radiotracers grouped by structural scaffold, including the Tauvid/flortaucipir family (A), other clinically used tracers such as MK-6240 (B), florzolotau analogues (C), and the OXD scaffold that produced both OXD-2115 and OXD-2314 (D). Reproduced from Lindberg, A., Murrell, E., Tong, J. et al. "Ligand-based design of [18F]OXD-2314 for PET imaging in non-Alzheimer's disease tauopathies." Nature Communications 15, 5109 (2024). https://doi.org/10.1038/s41467-024-49258-1. © The Author(s) 2024, licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

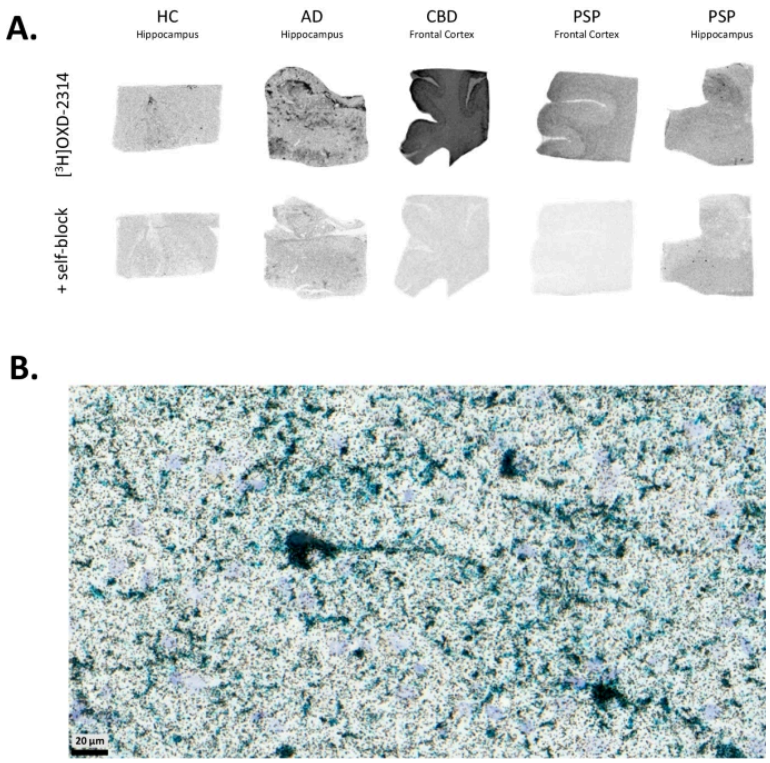

Figure 5. Autoradiographic binding of [3H]OXD-2314 in postmortem brain tissue. Panel A compares total binding (top row) against self-blocked, non-specific binding (bottom row) across healthy control (HC), Alzheimer's disease (AD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) tissue. Panel B shows high-resolution autoradiography in CBD cortical tissue, with OXD-2314 signal overlaid on AT8 phospho-tau immunohistochemistry. Note this experiment used AD, CBD, and PSP tissue rather than confirmed CTE tissue. Reproduced from Lindberg, A., Murrell, E., Tong, J. et al. "Ligand-based design of [18F]OXD-2314 for PET imaging in non-Alzheimer's disease tauopathies." Nature Communications 15, 5109 (2024). https://doi.org/10.1038/s41467-024-49258-1. © The Author(s) 2024, licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Regular brain scans (MRI)

Standard MRI scans in people with a history of head injuries often show a shrunken brain (atrophy), thinning of the outer brain layer, and that same enlarged cavum septum pellucidum mentioned earlier. The problem: these changes also show up with normal aging and with other brain diseases, so alone, these changes only raise suspicion rather than confirm anything.

A more specialized version, called diffusion MRI, tracks how water molecules move through brain tissue, which reveals damage to the brain's wiring that a normal scan misses. Some studies using this method have found unusual patterns in people with a history of repeated head impacts, though results are inconsistent across different studies. More recently, scientists have started feeding this diffusion data into machine learning models, letting a computer look for patterns across the whole scan rather than relying on a doctor eyeballing one section of wiring at a time.

Blood and spinal fluid tests

A blood test or spinal tap causes far less trauma than a brain scan, so researchers have been hunting for a chemical marker in blood or spinal fluid that flags CTE. A major study at Boston University, called DIAGNOSE CTE, found that former football players who met the TES criteria had lower levels of a protein called amyloid-beta in spinal fluid than players who did not meet the criteria. Oddly, tau levels in the spinal fluid did not differ between the two groups, meaning fluid tau alone does not serve as a reliable marker here, even though tau remains the protein driving the disease.

One protein that has shown more promise is GFAP (glial fibrillary acidic protein), released into the blood when support cells in the brain get injured. Higher GFAP levels have been linked to brain shrinkage and mental decline in people with repeated head impacts. That said, GFAP reflects general brain injury and inflammation, not CTE specifically, so GFAP alone cannot serve as a stand-alone test. Other candidate markers, including proteins tied to

inflammation, are still being studied. As of now, none of these fluid markers proves specific enough to CTE alone. Experts at a 2025 research summit concluded these tests currently work better for ruling out Alzheimer's disease than for ruling in CTE.

Machine learning synthesis

Since no single scan or blood test proves accurate enough alone, a growing number of researchers are trying to combine every available signal, brain scans, fluid markers, and a patient's history of head impacts, into one computer model that estimates the likelihood of CTE. This approach mirrors what has already worked well in Alzheimer's research, where models combining multiple types of data have outperformed any single test used alone. One review of 127 studies across several brain diseases found that these combined models can reach high accuracy under controlled research conditions, though accuracy consistently drops when a model trained on one group of patients gets tested on a different group, an important limitation worth keeping in mind.

Two specific techniques stand out. One uses an algorithm that reconstructs how the disease likely progressed in a person by comparing patterns across many cases, useful for understanding how the disease unfolds even before a scan-based test exists. The other trains a computer model to detect a history of repeated head impacts directly from brain scans, sidestepping the whole problem of needing confirmed CTE cases to train on, since exposure history proves much easier to confirm than the underlying disease. Not every attempt has worked, though. At least one major study that tried combining brain scan data alone, without fluid markers or exposure history, failed to reliably tell patients and healthy people apart, part of why the field has shifted toward combining several types of data rather than betting on scans alone.

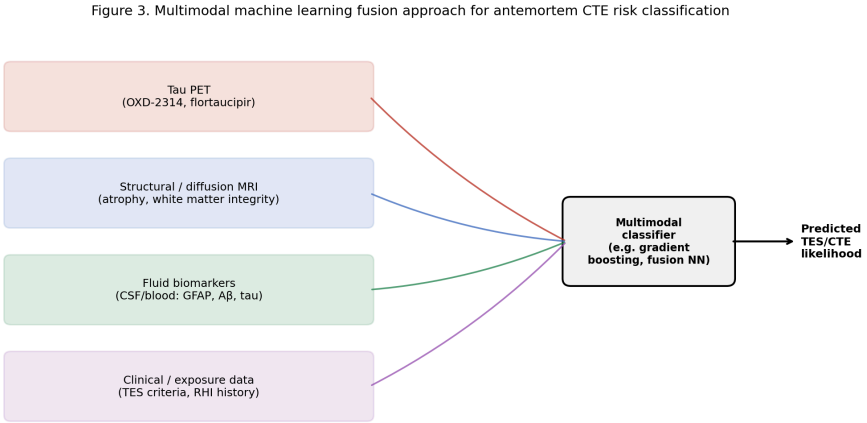

Figure 6. Rather than relying on any single marker, current classifier designs fuse tau PET, structural and diffusion MRI, fluid biomarkers, and clinical exposure data into one model. This mirrors the approach that has already outperformed single-modality classifiers in Alzheimer's disease research.

4. Discussion and Open Challenges

A chicken-and-egg problem sits at the center of this whole field. Every new test, whether a scan, a blood marker, or an AI model, needs checking against confirmed cases to prove the test works. But a confirmed case only exists after death. So almost every study testing a new tool has to work from suspected cases, or from the rare handful of people who happened to get brain scans years before death and later donated a brain for research. These overlap cases stay extremely rare, so studies confirming these tools tend to involve only a handful of people.

Telling CTE apart from Alzheimer's disease also proves genuinely difficult, and not just because scans lack sharpness. The two diseases can occur in the same brain at the same time, since a head injury independently raises a person's risk of later developing Alzheimer's disease. Doctors currently have no reliable way to figure out how much of a patient's memory loss comes from each disease.

Even the most promising tool covered here, the OXD-2314 scan, has only been tested in three suspected

CTE patients so far. That number falls nowhere near enough to know how well the scan will work across a broader population, with different ages, injury histories, and other health conditions layered in.

A research bias also deserves naming here. Almost all of the research in this area comes from studying former American football players, mostly because Boston University's long-running research program has focused on that group, and because football carries such a well-known public link to CTE. Boxers, soldiers, soccer players, and hockey players remain far less studied, even though the type and frequency of head impacts across these groups probably differs enough to affect how the disease shows up and how well any given test performs for each group.

Looking ahead, a follow-up study at Boston University called DIAGNOSE CTE Research Project-II is building on this earlier work, tracking participants for longer and adding more types of biomarkers, with results expected around 2029. The overall direction of the field seems clear: no single test is going to carry the full diagnostic weight alone, so the next few years will likely focus on testing these tools in larger, more diverse groups of people, and building the kind of large, shared datasets that AI models need in order to generalize instead of just memorizing quirks of one small group of patients.

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