Transcript Details
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Using fMRI to Identify Early Alzheimer's Disease Subgroups

Announcer:
You're listening to *Neurofrontiers* on ReachMD. On this episode, we'll hear from Dr. Hamid Abuwarda, who will be discussing his recent research on how brain connectivity patterns could help identify early subtypes of Alzheimer's disease. Dr. Abuwarda holds a PhD from Yale School of Medicine in New Haven, Connecticut, where he's currently an MD-PhD candidate. He recently presented this work as a poster at the 2025 CTAD conference.

Let's hear from Dr. Abuwarda now.

Dr. Abuwarda:
You know, the focus of this study, and really trying to understand preclinical Alzheimer's disease, is, in what ways can we use fMRIs to define the heterogeneity of the disease? So to kind of take a step back, preclinical Alzheimer's disease is really this insidious phase of the disease in which individuals can have evidence of biomarker elevation—and I'll come back to that idea of a biomarker—without any symptomatic presentations. It's thought to last anywhere from 10 to 20 years, and could be even longer. That's ongoing work. And the disease itself is really complicated by heterogeneity. And this is not unique to Alzheimer's or even dementia. This is really across medicine—how to really define heterogeneity of the disease—because not all of us present in the same ways. And so, especially in preclinical Alzheimer's disease—in which, again, individuals don't have symptoms—we're really leaning on these biomarkers.

So, basically, what we did was we took these functional connectivity measures and we tried to subtype this preclinical cohort of patients—so again, individuals who have evidence of the disease. And what we found is there were two major subtypes that were at least defined specifically by these functional connectivity measures. We found that there was no difference in cortical amyloid load, so if we looked at amyloid PET imaging, no difference between the two groups, and no difference between plasma biomarkers, which are thought to be really sensitive. But when we looked, again, no differences there, so these groups seem to primarily be defined by their functional connectivity values.

Now, the really cool part is, in a very exploratory way, we looked at how these individuals responded to solanezumab. So all of this was worked in an A4 study. This was a clinical trial of the solanezumab anti-amyloid drug, which unfortunately, failed. It did not show clinical benefit. But we wanted to ask, now that we've defined subtypes, were there differences between these groups in how they responded to the drug? And what we found is, yes, actually. One of the groups seemed to actually derive benefit from solanezumab and showed a decrease in cognitive decline over the course of the study. This was accompanied by differences in phospho-tau levels as well. So we're not just looking at cognitive metrics. We also found that there was an improvement of the phospho-tau trajectories over time as well, so we're seeing some biological effect with this group on solanezumab. Interestingly enough, there's actually no difference in amyloid clearance, which is a really thought-provoking finding. Solanezumab is an anti-amyloid drug. So we think it likely represents not differences in pathological load, but differences in underlying vulnerability and vulnerability that is defined by functional connectivity.

We wanted to really detail and try to better define these groups, so we looked at the underlying tau PET distribution—how did the tau pathology look within these groups? And we found that there were actually topologically very different tau PET distributions. The group that did derive benefit from solanezumab was actually a group that had very high levels of tau just across the cortex, so a very atypical distribution of tau that is not really reflected by the BRAAK staging. And especially this cortical predominant, this really coincides with a lot of the subtyping literature that has been done looking at tau PET and looking at pathology in postmortem brain tissue.

Announcer:
That was Dr. Hamid Abuwarda talking about strategies for identifying Alzheimer's subgroups before symptoms appear. To access this

and other episodes in our series, visit *Neurofrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!