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On Multiple Marker Analysis, Tangles Track Best With Functional Decline

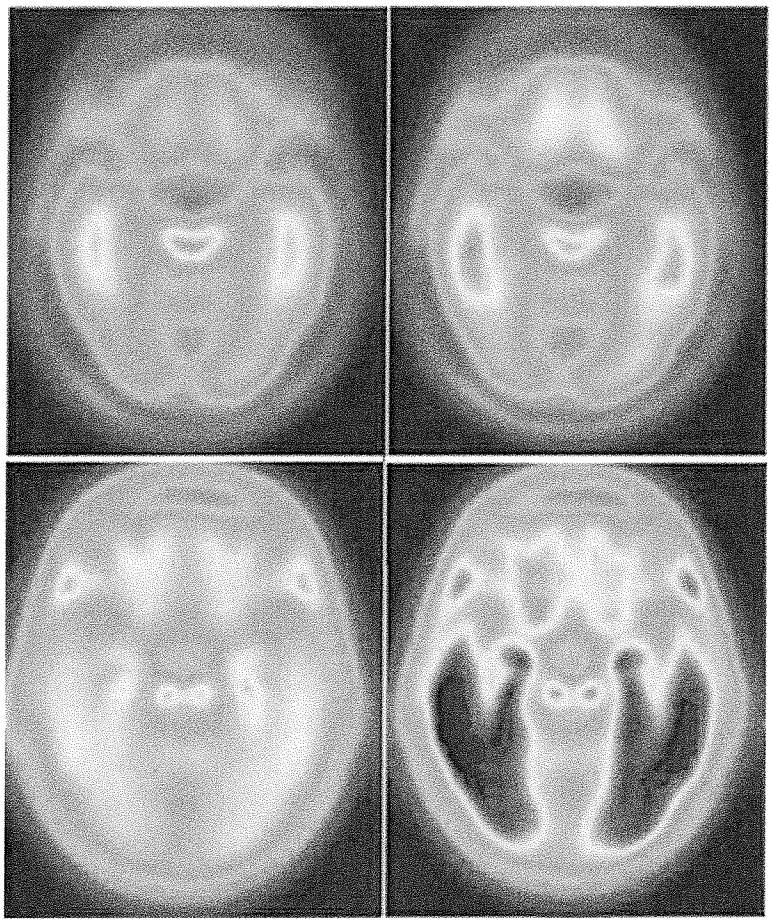
20 May 2016

In the past few years, tau imaging tracers have given researchers their first live look at the neurofibrillary tangles inside people's brains, visualizing where tau builds up in people who age normally or who develop a neurodegenerative disorder. How do tau patterns fit with more established markers of Alzheimer's disease (AD)? To find out, researchers led by Beau Ances and Tammie Benzinger at Washington University in St. Louis correlated tau imaging with amyloid PET, cerebrospinal fluid (CSF) measures of both amyloid and tau pathology, cognitive status, and neuropsychological measures among people with mild AD and age-matched normal controls. As reported in the May 11 Science Translational Medicine, distinct patterns of tau deposition in the brain best predict each one. The data help position tau positron emission tomography (tau-PET) data with more established AD biomarkers, and add to prior evidence that regional tau PET predicts cognitive decline better than amyloid-β. Spoiler alert: Even here, the relationship between amyloid and tau pathology is not simple or straightforward.

"This study represents a thoughtful advance in our understanding of the relations between early stage Alzheimer's disease pathology and both clinical and cognitive measures," wrote Samuel Lockhart, University of California, Berkeley, to Alzforum. "It confirms and extends other recent tau PET findings to start to break down the specific topographies of pathology that are critical to cognitive differences in late life." Lockhart was not involved in this work.

A few recent studies have taken Aβ and tau PET images from the same people. They so far support the old idea that of the two, tau is better at predicting cognitive decline (Johnson et al., 2016; Ossenkoppele et al., 2016). In addition, those studies suggest that in normal aging, tau builds up in the medial temporal lobe and episodic memory declines slightly, but when amyloid enters the picture, tau spreads out into the cerebral cortex and widespread cognitive impairment ensues (Mar 2016 news on Scholl et al., 2016). However, no paper had explored the region-to-region Aβ-to-tau PET associations. Nor had anyone matched up tau PET with Aβ imaging, CSF measures, and performance on neuropsychiatric tests all in the same people.

First author Matthew Brier and colleagues aimed to place neurofibrillary tangle deposition as per PET into staging diagrams. "There has been a lot of work starting to put these markers in a temporal order," said Ances. "We were interested in trying to figure out where tau PET fits in this progression, and how it relates to other biomarkers we have."

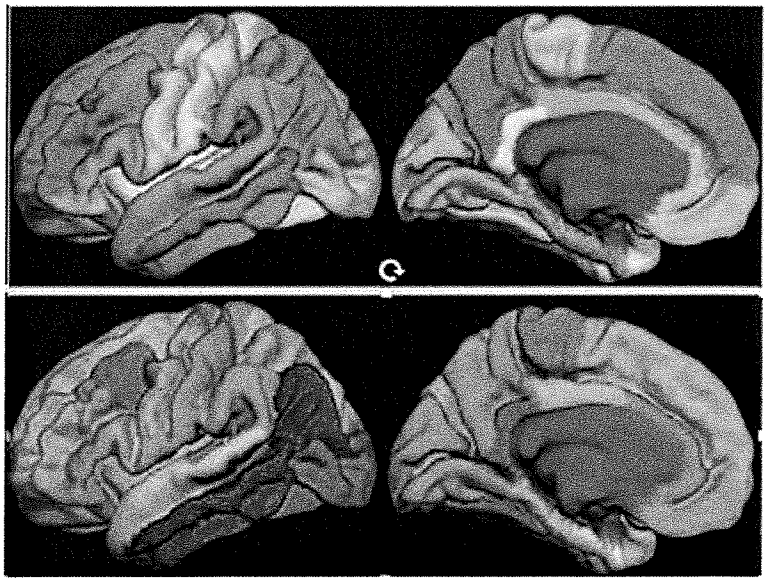


The difference is clear.

Differences between cognitively normal people (left) and cognitively impaired (right) are more obvious in tau PET scans (bottom) than in florbetapir PET images (top). [Courtesy of Beau Ances.]

The researchers recruited 46 people from the Knight Alzheimer's Disease Research Center at Washington University in St. Louis, average age 75. All were cognitively assessed using the clinical dementia rating scale (CDR). Thirty-six were cognitively healthy, 10 had been clinically diagnosed with either mild cognitive impairment (MCI) or mild AD. Each underwent PET scanning with T807 to image neurofibrillary tangles and florbetapir to visualize amyloid-β. Most participants also gave a CSF sample and took a series of neuropsychological tests, including those of semantic, episodic, visuospatial, and working memory.

As has been reported before, florbetapir uptake was already elevated in many of the healthy controls (see, for example, Crystal et al., 1988; Nov 2011 news). Brain amyloid deposition was lowest in those with normal CSF Aβ and tau, intermediate in those with abnormally low CSF Aβ, and highest in people with abnormal CSF Aβ and elevated CSF tau. This suggests amyloid deposition helps pick out patients who have CSF evidence of AD



Red Hot Trouble.

pathology from those who are still cognitively normal, Ances said.

In AD, Aβ in the frontal and parietal regions (top) tracks tau tangles in the medial temporal lobe, parietal cortex, and precuneus (bottom). Red/orange colors indicate more, blue less. [Courtesy of Science Translational Medicine/AAAS.]

By contrast, T807 scans revealed that cognitively normal people had little fibrillar tau in the brain, except some in the basal ganglia. In those who were slightly cognitive impaired, however, insoluble tau appeared to have risen and spread. In people diagnosed with MCI or mild AD, tau had accumulated in the temporal lobes and throughout the cerebral cortex. This tangle burden associated more strongly with cognitive status than did amyloid load (see image above).

What's more, where tau was deposited in the brain tau tracked better with declining neuropsychological test scores. Tau deposits in temporal and basal frontal regions coincided with declining semantic, visuospatial, and global memory. The predictive value of florbetapir uptake was much weaker. "The results fit with the idea that amyloid is among the earliest changes going on in AD; it goes up and stays elevated before cognitive impairment," Ances told Alzforum. "Later on, in the transition to MCI or symptomatic AD, that's where tau fits in."

Using multivariate analysis, Brier and colleagues identified a disease-related regional distribution pattern, aka topography, for Aβ, and one for tau. These patterns of covariance tracked with disease, being found only in people with MCI or AD. For Aβ, this topography included primarily frontal and parietal regions; for tau, the temporal lobe including the hippocampus.

Given that these Aβ and tau topographies differed, the authors wondered if there was any relationship between the accumulation of Aβ in one area, and tau in another. They found that in people with mild AD, frontal and parietal Aβ highly correlated with tau in the medial temporal lobe, parietal cortex, and precuneus (see image above). "This is telling us that both of these pathologies contribute to disease progression and are related to each other, but [as seen above] tau tracks cognitive symptoms more closely," wrote Brier to Alzforum.

How are these correlated distributions of Aβ and tau tied together? "That's the million-dollar question," said Ances. "It may be that Aβ-affected regions are physically connected to tau-affected regions, or maybe they are connected in a different way." The results reveal intermediate stages of tau progression rarely seen in neuropathology studies. In some people, tau has spread into lateral, temporal, parietal, and even occipital areas while the person was still cognitively normal, Ances said. The scientists still don't know what causes tau to spread, and how the relationships between tau, Aβ imaging, CSF, and cognition change over time.

Historically, researchers have had no luck correlating amyloid plaque burden to cognitive decline. This new data suggest that amyloid can give some information about cognitive status, but less than tau. "At the extremes, it's very useful; if someone has no Aβ, they don't have AD, and if they have a lot of Aβ, they likely have severe AD," noted Brier. "But tau gives a better prediction of cognition using a smaller number of brain regions," he wrote.

The researchers also used a type of regression analyses to examine which regions of Aβ and tau deposition best predicted CSF measures of AD pathology. Aβ deposits in the frontal and parietal regions predicted lower CSF Aβ42. Tau tangles in the entorhinal and temporal cortices, as well as the cuneus, best predicted higher CSF tau. Interestingly, florbetapir uptake in the frontal and temporal regions also predicted elevated CSF tau. This suggested to the authors that tau pathology depends initially on the presence of Aβ.

The data fit with the idea that amyloid accumulation precedes tau pathology, and that large amounts of amyloid plus the spread of tau outside of the medial temporal lobe trigger the progression of disease, said Ances. He said the study largely confirms the temporal order of Alzheimer's biomarkers proposed by Cliff Jack from the Mayo Clinic, Rochester, Minnesota (Jack et al., 2010; Feb 2013 news). In other words, amyloid accumulates first, followed by tau, and the resulting assault on synaptic communication leads to cognitive decline.

"This study found that while amyloid and tau are clearly related to each other, they are separated in space, with different brain regions showing an early proclivity for each pathology," wrote Gil Rabinovici, University of California, San Francisco, to Alzforum. "Though we have known about this paradox for some time from neuropathology studies, the imaging findings highlight the need to integrate these findings into unifying models of AD that will better explain how amyloid and tau interact with each other and synergize to drive disease," he wrote. Rabinovici said he would have liked to see a measure of neurodegeneration included, such as MRI, as it may mediate the relationship between tau deposition and cognitive decline. He also pointed out that the data are heavily weighted toward normal older people. Since the relationships between tau PET and other imaging, cognitive, and CSF variables probably vary across disease stages, it will be interesting to sample a larger number of patients with MCI and AD dementia, he said.—Gwyneth Dickey Zakaib

COMMENTS

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Comments on this content

Laure Saint-Aubert
Karolinska Institutet

Posted: 24 May 2016

In this paper, Brier and colleagues investigated the topography of in vivo tau and Aβ deposition in a multimodal setting.

This new study offers interesting and innovative approaches to investigate the regional pattern of the pathological markers of Alzheimer's disease in vivo, and their relationship with other key biomarkers. Interestingly, the authors showed that tau and Aβ deposition (as measured by ^{18}F-T807 and ^{18}F-florbetapir, respectively), while exhibiting different patterns, correlate together in distinct combinations of regions ("topographies"). Of course their findings will need to be replicated in larger cohorts.

The strength of this study is the multivariate approach, not only using PET imaging but also CSF as well as cognitive measurements. In a research field where the underlying mechanisms triggering the symptoms are not yet understood, it appears fundamental to look at combinations of actors instead of single variables, in order to comprehend the whole pathogenic process.

The participants in this study underwent exhaustive neuropsychological testing, allowing the authors to determine whether the regional tau deposition could predict the performance in several cognitive domains. They found that tau deposition pattern predicted cognition performance better than Aβ deposition did. It cannot, however, be excluded that these associations with cognition might be driven by the few AD patients included in the study (no association remained when looking at the cognitively normal population only). This illustrates nonetheless the importance of looking at cognition in greater details, and not considering MMSE or other simplistic measures as a good (sensitive enough) assessment tools for cognition.

This should be considered as more a study on normal aging than disease, since most participants are cognitively normal volunteers (36 out of the 46 participants). There has been an increasing interest in assessing tau deposition in normal elderly subjects. Brier and colleagues' findings are in agreement overall with a recent report on cognitively normal subjects using the same tau tracer (Johnson et al., 2016).

The authors were also able to compare ^{18}F-T807 and ^{18}F-florbetapir PET imaging findings with CSF biomarkers. Such investigations are, of course, highly valuable, and the rather intriguing results reported in the paper will hopefully raise more attention and discussion from the scientific community.

Several crucial questions regarding tau imaging that could not be addressed by this study remain open, the most important one being whether the signal we observe in PET is specific of tau pathology, or whether we might be targeting additional unknown features. There has been active discussion on this topic, and while in vitro analyses show good affinity from the tau tracers to their target (Feb 2016 news), their specificity and the correspondence between in vitro and in vivo signal remain unclear. The development of tau tracers offers exciting opportunities, and, hopefully, with the help of in vitro work and future multimodal studies like the present one, we will crack the code of AD's pathological cascade.

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Gil Rabinovici
UCSF

Posted: 24 May 2016

The ability to study the interplay between Aβ and tau in vivo across the aging-to-AD spectrum is incredibly exciting and in my opinion highly likely to yield new insights into disease mechanisms. This study adds to a growing literature on this topic (e.g. Johnson et al., 2016; Scholl et al., 2016; Ossenkoppele et al., 2016).

This study took a unique approach to identifying spatial patterns of Aβ (florbetapir) and tau (T807) deposition and found that while amyloid and tau are clearly related to each other, they are separated in space, with different brain regions showing an early proclivity for each pathology. Though we have known about this paradox for some time from neuropathology studies, the imaging findings highlight the need to integrate these findings into unifying models of AD that will better explain how amyloid and tau interact with each other and synergize to drive disease.

As with previous studies, the authors found that cognitive performance is more strongly related to tau than amyloid. A missing piece in this particular study is a measure of neurodegeneration (e.g. MRI), which may mediate the relationship between tau deposition and cognitive decline.

This is also one of the first studies to assess the relationships between tau PET and CSF measures of total tau and p-tau. The initial findings suggest that these relationships are not as straightforward as the inverse relationship between CSF and PET measures of Aβ, and require further study.

One limitation of the present study is that it is quite heavily weighted toward normal older individuals (75 percent of subjects with CDR=0). The relationships between tau PET and other imaging, cognitive, and CSF variables will likely vary across disease stages, and sampling a larger number of patients with MCI and AD dementia will be informative in this respect.

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Samuel Lockhart

Posted: 24 May 2016

This study by Brier et al. represents a thoughtful advance in our understanding of the relations between early stage Alzheimer's disease pathology, measured using PET and CSF measures for amyloid as well as tau, and both clinical and cognitive measures. This study confirms and extends other recent AV-1451/T807 tau PET findings—to start to break down the specific topographies of pathology that are critical to brain and cognitive differences in late life (Johnson et al., 2016; Ossenkoppele et al., 2016; Schwarz et al. 2016; Schöll et al., 2016). The authors provide a useful next step toward taking greater advantage of the specificity of tau imaging, to start to convey topographical information of these relations. I appreciated the methodological approaches the authors used: singular value decomposition to summarize complex PET spatial patterns, canonical correlation to simplify amyloid-tau relations, and penalized regressions for relating PET/CSF with cognition. This paper helps lead me to ask the next questions, such as: What are the more specific patterns of spatial relations between amyloid and tau PET? Are there different temporal trajectories of topographies across people or across the brain? And lastly, how does the pattern of these relations, particularly in normal elderly, speak to the biological relationships between amyloid and tau pathologies?

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FURTHER READING

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