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Is tau imaging more than just "upside-down" FDG imaging?

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Several neurodegenerative disorders exhibit pathological aggregation of the tau-protein in the brain and are therefore summarized under the term "tauopathies"*(1)*. Alzheimer's disease (AD) is considered a tauopathy, because in addition to extraneuronal ß-amyloid plaques, it is characterized by pathological tau-aggregation in form of intraneuronal neurofibrillary tangles *(2)*. In other tauopathies - including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and some other disorders of the spectrum of frontotemporal lobar degenerative disorders- tau pathology may occur as the leading form of protein aggregation abnormality *(3).* The disappointing results of anti-amyloid therapy approaches in AD *(4,5)* and the onset of novel anti-tau therapeutical concepts *(6,7)* have increased the interest in *in vivo* detection of tau pathology, which was limited to post-mortem examinations so far.

Several PET tracers for cerebral tau deposits have been developed and some have already been applied *in vivo* in patients with neurodegenerative disorders. The most widely used tracers are 18F-AV-1451, 18F-THK5351 and 11C-PBB3 (8,9). More recently, tracers such as 18F-MK-6240, 18F-RO6958948, [18F]PI-2620 and 18F-JNJ64349311 have been introduced and further compounds are under evaluation *(10–12)*. Although some of these compounds are already being tested in clinical trials (up to phase 3), currently, all of the available tracers can still be considered in an exploratory stage and the available literature is still limited.

In several studies, a strong similarity between the distribution of tau-tracer retention in the brain and the extent of hypometabolic abnormalities (as measured with 18F-FDG-PET) has been observed (Fig.1) *(13–16)*. Furthermore, these studies statistically demonstrated an inverse quantitative relationship between tau-deposition and metabolism. While underscoring the hypothesis that tau pathology may be causally involved in the development of neuronal dysfunction, this "upside down" similarity between the two methods raises the question if tau-PET has additional clinical value over established 18F-FDG-PET imaging.

STATUS OF TRACER VALIDATION

18F-FDG PET imaging has proven high diagnostic value at relatively low costs in the assessment of neurodegeneration *(17–21)*. The tracer is broadly available, automated analytical approaches and international guidelines are established *(20,21)*.

In contrast, validation and standardization of tau-tracers is far less advanced. This may stem not only from the novelty of the tracers but also from the complexity of tau as a target itself. Tau-deposition can occur in different splicing isoforms (3R vs. 4R), different primary forms of fibrous assembly (paired helical vs. straight filaments), and different aggregation states (neurofibrils, pretangles, mature tangles, coiled bodies, etc.). Moreover, tau can be found in different cellular (intraneuronal, intraglial) and macroscopic anatomical locations (basal ganglia/cortex) *(22,23)*. This variance in the appearance of tau-pathology hampers the development and evaluation of tau-imaging tracers.

Recently developed tau-tracer have been promising in so far, as *in vitro* analyses suggested distinct binding to tau pathology in absence of relevant binding to amyloid *(8)*. Furthermore, in vivo tracer retention patterns showed good agreement with the expected distribution of tau-pathology *(2,24)*. However, considerable between-tracer differences in regional capture of tau pathology may exist in AD *(25–27)* and in non-AD tauopathies such as CBD or PSP. Additionally, some evidence questions the specificity of currently available tau tracers. This refers to non-tau pathology such as TDP-43 and to "off-target" binding which has been observed in vivo for several of the tracers in various regions (basal ganglia, brain stem, choroid plexus and extracerebral structures) *(24,28,29)*

Elevated binding to melanin and monoaminooxidase (MAO) may explain part of the latter findings *(30–32)*. Particularly worrisome are recent findings, demonstrating a potential contribution of MAO-B binding to tau PET imaging not only in subcortical but also in cortical brain regions (31). Such a contribution of unspecific binding could hamper quantitative assessment, particularly in longitudinal tau-PET studies.

In summary, comparability between existing tau-tracers is currently not warranted. To gain critical insight into the differential sensitivity and specificity of the currently available tracers, further evaluation is required, particularly with regard to systematic in vivo/post mortem cross validation. Corresponding studies are currently underway.

POTENTIAL FOR EARLY DIAGNOSIS:

The value of 18F-FDG PET for early diagnosis of AD particularly regarding short-term prediction of conversion to AD-type dementia in patients with mild cognitive impairment has been repeatedly demonstrated *(20,34,35)*. Similar data is not yet available for tau-PET imaging. Supporting current hypothetical disease models, some studies suggest that tau- pathology may be detected subsequent to elevated amyloid-pathology by means of amyloid-PET *(36)*. Others

suggest that mesial temporal tau-aggregation may exist in some healthy elderly subjects in the absence of amyloid-pathology, but pathological relevance of these findings is yet unclear *(24)*. Regarding the obvious similarity between 18F-FDG-PET and tau-PET findings documented so far, similar sensitivities with regard to early detection may be expected. However, preliminary data from our and other groups (directly comparing 18F-FDG- and tau-PET in patients with mild cognitive impairment and AD) suggest that tau-abnormalities may be somewhat more pronounced than hypometabolic changes and possibly could be detected earlier (Fig.2) *(37)*.

POTENTIAL FOR DIFFERENTIAL DIAGNOSIS:

The valuable role of 18F-FDG-PET in differential diagnosis of neurodegenerative disorder has repeatedly been demonstrated, including differentiating various forms of dementia but also different forms of movement disorders/atypical Parkinsonian syndromes *(38,39)*. In a similar vein, tau-PET imaging shows specific patterns of tau-tracer retention in typical and atypical variants of AD and other tauopathies *(14,15,40-43)*. However other than 18F-FDG, tau-PET at the same time provides insights on underlying neuropathology which may allow to distinguish tauopathies (e.g. CBD or PSP) from non-tauopathies (e.g., multiple system atrophy).

POTENTIAL AS A BIOMARKER IN CLINICAL TRIALS:

For 18F-FDG-PET, a reliable association between hypometabolism and the type and severity of cognitive deficits has been demonstrated *(44,45)*. This qualifies 18F-FDG-PET as a valuable tool to track clinical progression. However, 18F-FDG-PET results may be affected by functional processes such as diaschisis or compensatory effects. In this respect, tau-imaging may more directly mirror the extent and progression of neuropathology. Moreover, as a major advantage over amyloid-PET, tau tracer uptake may better track cognitive decline than amyloid deposition, as expected from neuropathological studies. Most importantly, tau-PET may be used for the selection of patients in future therapeutic trials directed towards the removal of tau-pathology *(7)*. Results from tau-PET may also serve as a surrogate endpoint in clinical trials, since tau-PET may reflect more proximal processes in the cascade of neurodegeneration than hypometabolism. It could therefore excel FDG-PET as a “reasonably likely surrogate endpoint” in clinical trials *(46)*.

CONCLUSION:

Tau-imaging represents an exciting novel approach, aiming to assess a basic pathology of neurodegeneration *in vivo.* Although similarities between patterns of hypometabolism and tau tracer deposition have been documented, tau-imaging certainly offers more than just “upside-down” 18F-FDG-PET information. An added clinical value of tau-PET imaging over well-established 18F-FDG-PET can be expected but remains to be proven. Preliminary data indicates that tau-imaging could be slightly more sensitive than 18F-FDG-PET to detect the onset of neuronal injury in early stages of AD. In addition, tau-PET may have advantages with regard to differential diagnosis. In addition to measuring extent and localization of pathology, tau-PET may allow to differentiate between tauopathies and non-tauopathies. These questions may gain relevance with the advent of anti-tau therapy trials. Specific monitoring of anti-tau treatment may also represent a most important future application for tau-PET. While tau-PET imaging certainly holds great potential in various diseases and in different domains spanning from early and differential diagnosis to disease monitoring, many questions particularly with regard to

validation of the tracer still remainopen. Much more needs to be learned about the variability of the signal due to unspecific contributions, across different tracers, and in different disease populations.

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Figure Captions:

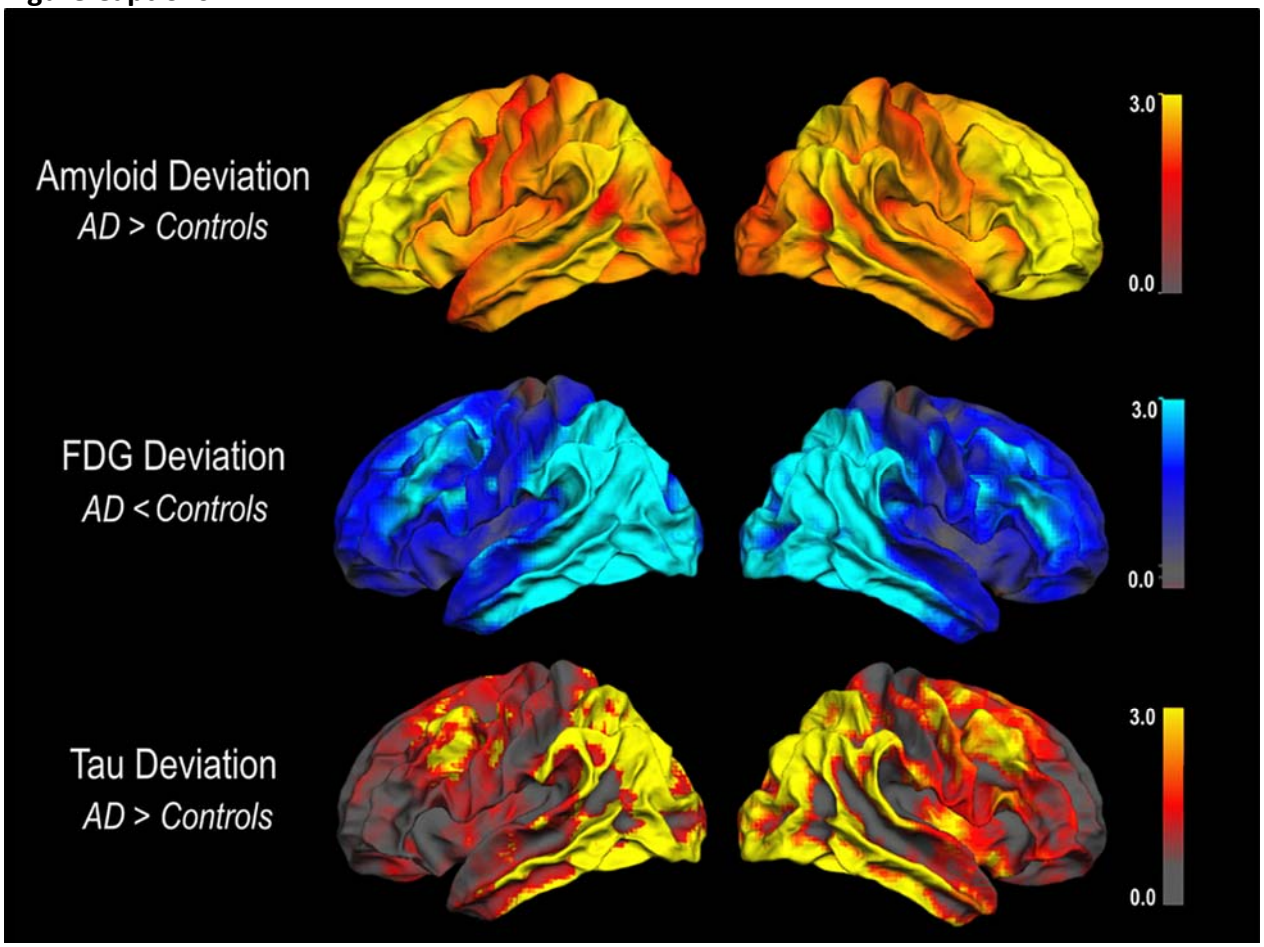

Figure 1: Spatial correspondence of mean 18F-FDG deviation (middle row) and mean tau deviation (bottom row) but not amyloid deviation (top row) in patients with Alzheimer's disease (AD). Deviation images were projected on the lateral surface of the left and the right hemisphere using FreeSurfer. With permission from [13]

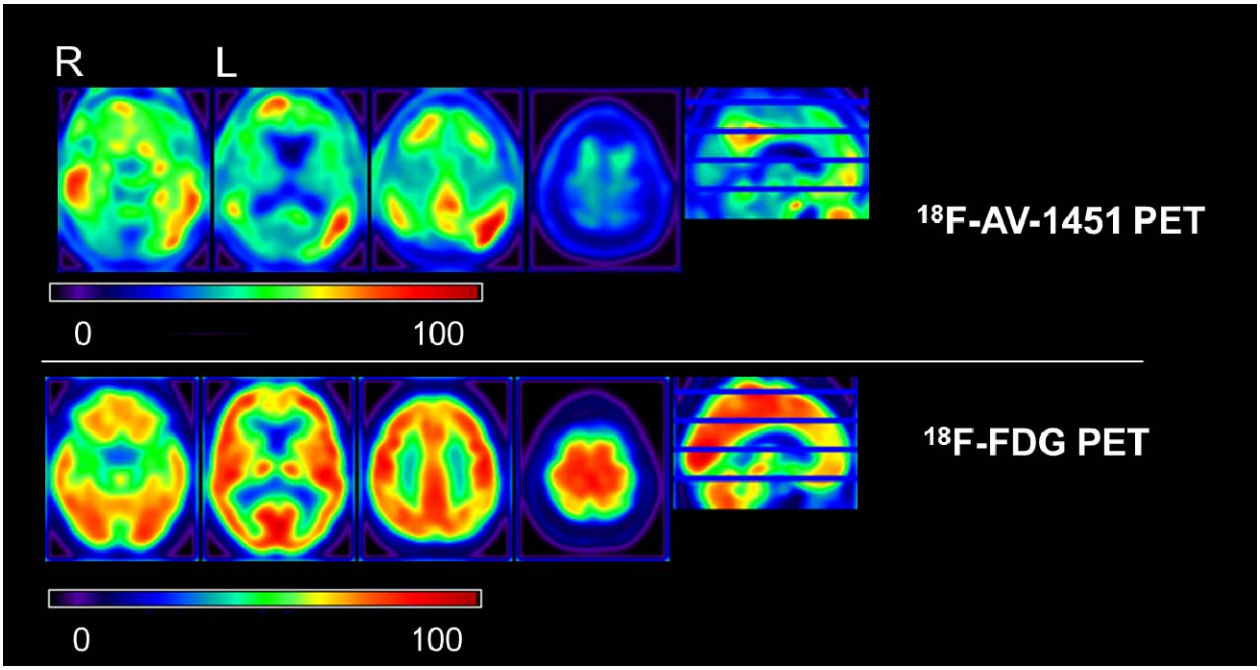

Figure 2: Clearly abnormal Tau-PET, but barely abnormal 18F-FDG-PET in a 66-year-old man with mild cognitive impairment and CSF values indicative of Alzheimer's disease (AD) pathology. Axial slices of Standard-Uptake-Value-Ratio (SUVR) images for 18F-AV-1451 (top row) and 18F-FDG (bottom row) PET. Global maximum intensities were set to 100 for intensity scaling. R, right; L, left.