ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-12

Alzheimer's & Dementia

Featured Article

# Longitudinal uncoupling of cerebral perfusion, glucose metabolism, and tau deposition in Alzheimer's disease

Antoine Leuzy[a], Elena Rodriguez-Vieitez[a], Laure Saint-Aubert[a], Konstantinos Chiotis[a], Ove Almkvist[a,b,c], Irina Savitcheva[d], My Jonasson[e,f], Mark Lubberink[e,f], Anders Wall[e,g], Gunnar Antoni[g,h], Agneta Nordberg[a,b,*]

[a]*Division of Translational Alzheimer Neurobiology, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden*
[b]*Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden*
[c]*Department of Psychology, Stockholm University, Stockholm, Sweden*
[d]*Department of Radiology, Karolinska University Hospital Huddinge, Stockholm, Sweden*
[e]*Department of Surgical Sciences, Radiology, Uppsala University, Uppsala, Sweden*
[f]*Medical Physics, Uppsala University Hospital, Uppsala, Sweden*
[g]*PET Centre, Uppsala University Hospital, Uppsala, Sweden*
[h]*Department of Medicinal Chemistry, Uppsala University, Uppsala, Sweden*

**Abstract**

**Introduction:** Cross-sectional findings using the tau tracer [$^{18}$F]THK5317 (THK5317) have shown that [$^{18}$F]fluorodeoxyglucose (FDG) positron emission tomography data can be approximated using perfusion measures (early-frame standardized uptake value ratio; ratio of tracer delivery in target to reference regions). In this way, a single positron emission tomography study can provide both functional and molecular information.

**Methods:** We included 16 patients with Alzheimer's disease who completed follow-up THK5317 and FDG studies 17 months after baseline investigations. Linear mixed-effects models and annual percentage change maps were used to examine longitudinal change.

**Results:** Limited spatial overlap was observed between areas showing declines in THK5317 perfusion measures and FDG. Minimal overlap was seen between areas showing functional change and those showing increased retention of THK5317.

**Discussion:** Our findings suggest a spatiotemporal offset between functional changes and tau pathology and a partial uncoupling between perfusion and metabolism, possibly as a function of Alzheimer's disease severity.



*Keywords:* Positron emission tomography (PET); Tau imaging; THK5317; Neurofibrillary tangles; FDG; Hypometabolism; Perfusion imaging; $R_1$; Perfusion SUVR; Alzheimer's disease; Prodromal Alzheimer's disease; Alzheimer's disease dementia; Mild cognitive impairment; Longitudinal study

## 1. Introduction

In addition to amyloid-β (Aβ) and tau pathology, Alzheimer's disease (AD) is characterized by decreased brain perfusion [1,2] and glucose metabolism [3,4]. Cross-sectional comparative studies have indeed shown regional perfusion and metabolism to be tightly coupled in neurodegenerative disorders, including AD [5,6], and in controls, under both active and resting physiological conditions [7]. As such, [$^{18}$F]fluorodeoxyglucose (FDG) positron emission tomography (PET) metabolic data can be approximated using early-frame standardized uptake value ratio (p-SUVR) and the ratio of tracer delivery in target ($K_1$) and reference regions ($R_1$), measures shown to correlate strongly with brain perfusion [8,9].

*Corresponding author. Tel.: +46 8 585 85467; Fax: +46 8 585 85470.
E-mail address: agneta.k.nordberg@ki.se

https://doi.org/10.1016/j.jalz.2017.11.008

Comprehensive compartmental approaches, involving the solution of differential equations and requiring arterial blood sampling, form the basis of PET-based estimation of physiological parameters of interest [10]. Reduced configuration models have been developed, however, whereby the input function derived from arterial plasma is replaced by that from a reference region [10]. These approaches obviate the need for arterial cannulation and metabolite assay, simplifying scanning protocols and data analysis procedures. While the objective of these models is to obtain an estimate of tracer binding, such as the distribution volume ratio (DVR)—total distribution volume in target over reference region—derived from reference Logan, a graphical approach involving linearization [11], perfusion information in the form of $R_1$ can also be obtained using models that rely on iterative curve fitting such as the simplified reference tissue model [12] and related approaches involving parameter coupling [13]. By contrast, calculation of p-SUVR does not require kinetic modeling and instead reflects the assumption that early–time frame uptake reflects $K_1$ [14], with p-SUVR thus reflective of $R_1$.

Findings from studies implementing the use of perfusion measures (p-SUVR and $R_1$) with Aβ PET tracers have shown to closely correlate with FDG, and to carry potential clinical utility, having been used to distinguish AD from controls [15], frontotemporal lobar degeneration [16], and cerebral amyloid angiopathy [17]. Findings from our earlier cross-sectional study using, the tau-specific PET tracer [$^{18}$F] THK5317 (THK5317) [18,19] in AD suggest that tau imaging may also prove able to provide both molecular and functional information [9], similar to that proposed for Aβ PET [16]. Given the possible future clinical use of tau PET for diagnostic purposes and evaluation of drug therapies, as well as the advantages inherent to dual-use imaging [20,21], further exploration of these findings is warranted.

In this study, we sought to quantify the longitudinal relationship between THK5317 perfusion measures, glucose metabolism (FDG SUVR), and tau pathology (THK5317 DVR), in a cohort of patients with AD. The test-retest reproducibility of THK5317 perfusion measures was likewise investigated.

## 2. Methods

### 2.1. Participants

Sixteen AD patients (10 prodromal AD and six AD dementia) who had previously participated in baseline investigations [22,23] were here followed up after a median interval of 17 months (interquartile range: 15–18 months) [24]. All patients had originally undergone clinical assessment for memory problems at the Department of Geriatric Medicine, Karolinska University Hospital, Huddinge, Sweden, and had been followed up after diagnosis, as detailed elsewhere [22]. Patients diagnosed with AD dementia met the revised NINCDS-ADRDA criteria for probable AD and showed in vivo evidence of AD pathology (abnormal [$^{11}$C] Pittsburgh Compound B [PIB]) [25]. Patients who fulfilled the diagnosis of mild cognitive impairment [26] and showed a positive PIB scan were diagnosed as prodromal AD [27].

All subjects provided informed consent to take part in the present study, which was conducted according to the Declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional human ethics committee of Stockholm and the Faculty of Medicine and Radiation Hazard Ethics Committee of Uppsala University Hospital, Uppsala, Sweden.

### 2.2. Acquisition and analysis of imaging data

Dynamic THK5317 studies were conducted over 60 minutes, following intravenous bolus injection of 217 ± 42 MBq. A static 15-minute FDG scan was performed 30 minutes after injection of 3 MBq/kg. Dynamic baseline and follow-up THK5317 and FDG PET images were coregistered to their respective T1-MRIs using PMOD (v.3.5; PMOD Technologies Ltd., Zurich, Switzerland). Structural images were segmented using SPM8, with the inverse transformation parameters generated used to spatially warp a probabilistic atlas [28] into native T1 image space. Voxelwise THK5317 p-SUVR and simplified reference tissue model $R_1$ maps were obtained with PMOD, using the cerebellar cortex as reference tissue [9,12]. For p-SUVR, the interval 0–3 minutes was selected based on the previously reported observation that this interval showed the highest correlations with FDG [9]. Parametric SUVR (30–45 minutes) and Logan DVR images (30–60 minutes) were created for FDG and THK5317, respectively, using the cerebellar cortex as reference region [11,22].

Annual percentage change was calculated voxelwise for all PET parameters as follows: {[(Follow-up − Baseline)/Baseline]/Time interval between scans (years)} × 100%. To binarize resulting parametric maps to examine their spatial overlap, average isocortical test-retest reproducibility of THK5317 perfusion measures (rounded) was adopted to exclude voxels within the test-retest repeatability range of perfusion measures. Voxelwise THK5317 p-SUVR, $R_1$, and FDG SUVR maps were used to perform pairwise correlations using the biological parametric mapping software package (MATLAB v.3.3). An 8-mm filter and an a priori gray matter mask were then applied to spatially normalized PET images with resulting correlation maps thresholded at $P < .001$ (uncorrected, cluster extent ≥ 20 voxels).

### 2.3. Test-retest reproducibility of THK5317 perfusion measures

To establish the test-retest reproducibility of THK5317 p-SUVR and $R_1$, five subjects (four prodromal AD and one possible corticobasal syndrome) [29] underwent a retest THK5317 PET scan (range: 13–37 days).