Patients with Alzheimer’s disease can present with different clinical phenotypes. Individuals with late-onset Alzheimer’s disease (>65 years) typically present with medial temporal lobe neurodegeneration and predominantly amnestic symptomatology, while patients with early-onset Alzheimer’s disease (<65 years) exhibit greater neocortical involvement associated with a clinical presentation including dyspraxia, executive dysfunction, or visuospatial impairment. We recruited 20 patients with early-onset Alzheimer’s disease, 21 with late-onset Alzheimer’s disease, three with prodromal early-onset Alzheimer’s disease and 13 with prodromal late-onset Alzheimer’s disease, as well as 30 cognitively healthy elderly controls, that had undergone 18F-AV-1451 tau positron emission tomography and structural magnetic resonance imaging to explore whether early- and late-onset Alzheimer’s disease exhibit differential regional tau pathology and atrophy patterns. Strong associations of lower age at symptom onset with higher 18F-AV-1451 uptake were observed in several neocortical regions, while higher age did not yield positive associations in neither patient group. Comparing patients with early-onset Alzheimer’s disease with controls resulted in significantly higher 18F-AV-1451 retention throughout the neocortex, while comparing healthy controls with late-onset Alzheimer’s disease patients yielded a distinct pattern of higher 18F-AV-1451 retention, predominantly confined to temporal lobe regions. When compared against each other, the early-onset Alzheimer’s disease group exhibited greater uptake than the late-onset group in prefrontal and premotor, as well as in inferior parietal cortex. These preliminary findings indicate that age may constitute an important contributor to Alzheimer’s disease heterogeneity highlighting the potential of tau positron emission tomography to capture phenotypic variation across patients with Alzheimer’s disease.
Introduction

Alzheimer’s disease typically presents at old age, i.e. ≥65 years (late-onset Alzheimer’s disease) and predominantly with amnestic deficits (Scheltens et al., 2016). Approximately 5–10% of patients with Alzheimer’s disease, however, show a dementia syndrome prior to age 65 (i.e. early-onset Alzheimer’s disease) (Barkhof et al., 2007). Although amyloid-β plaques and tau neurofibrillary tangle pathology underlie both late-onset and early-onset Alzheimer’s disease, there are remarkable differences in the neurodegenerative patterns and clinical symptomatology. The neuropsychological profile of patients with early-onset Alzheimer’s disease is heterogeneous and includes more often than in late-onset Alzheimer’s disease non-amnestic features such as executive, language or visuo-spatial dysfunction (Koss et al., 1996). Furthermore, patients with early-onset Alzheimer’s disease show a more aggressive disease course, illustrated by faster rates of cognitive decline and shorter survival after time of diagnosis (Koedam et al., 2008). These phenotypic differences corroborate with brain atrophy and glucose hypometabolic patterns that are distinct in extent (early-onset Alzheimer’s disease > late-onset Alzheimer’s disease) and location, with early-onset Alzheimer’s disease generally demonstrating neocortical predominance and late-onset exhibiting medial temporal lobe vulnerability (Frisoni et al., 2007; Rabinovici et al., 2010; Ossenkoppele et al., 2012). Finally, autopsy studies have indicated that patients with early-onset Alzheimer’s disease harbour greater pathological burden (amyloid-β and tau) than their late-onset counterparts, more consistently, however, for tangle than plaque pathology (Berg et al., 1998; Ho et al., 2002).

The advent of 18F-AV-1451, a PET tracer with high affinity to detect paired helical filament tau, provides the unique opportunity to examine neurofibrillary tangle load in vivo (Chien et al., 2013). Computationally extracting detailed regional information with full brain coverage is a major advantage of neuroimaging over neuropathologic data that generally includes only a few slices in a small number of brain areas with a long interval between disease onset and autopsy. Furthermore, post-mortem early-onset versus late-onset Alzheimer’s disease studies may be systematically biased as the increased pathological burden in early-onset Alzheimer’s disease may be explained by a more advanced stage of the disease at time of death as patients with late-onset Alzheimer’s disease more frequently die due to other age-related conditions. In the present study, we therefore sought to examine in vivo differences in tau pathology in living early-onset and late-onset Alzheimer’s disease patients. We hypothesized that patients with early-onset Alzheimer’s disease would show more pronounced neocortical 18F-AV-1451 retention, while 18F-AV-1451 uptake in patients with late-onset Alzheimer’s disease would be more expressed in (medial) temporal regions.

Materials and methods

Participants

Participants were recruited from the prospective and longitudinal Swedish BioFINDER study (www.biofinder.se). Thirty cognitively healthy elderly participants (healthy controls) were included if they met inclusion criteria age ≥60 years, ≥28 points on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) at the screening visit, no cognitive symptoms as evaluated by a physician, fluency in Swedish, no fulfilment of the criteria for mild cognitive impairment (MCI) or any dementia. Exclusion criteria included presence of significant neurologic or psychiatric disease, significant systemic illness, and significant alcohol abuse. We further included 16 patients with prodromal Alzheimer’s disease (MCI due to Alzheimer’s disease; three early-onset, 13 late-onset), who were recruited at the Memory Clinic, Skåne University Hospital and were referred to the memory clinics because of cognitive impairment, did not fulfil the criteria for dementia, had an MMSE score of 24–30 points, objective memory impairment according to delayed word list recall, were aged 60–80 years, had low CSF amyloid-β42 levels, and were fluent in Swedish. Exclusion criteria were cognitive impairment explained by another condition, significant systemic illness making it difficult to participate, refusing lumbar puncture, or significant alcohol abuse. Lastly, 41 patients with Alzheimer’s disease, whereof 20 early- and 21 late-onset, were included after assessment by a medical doctor specialized in dementia disorders. They met the DSM-IIIIR criteria for dementia (American Psychiatric Association and American Psychiatric Association Work Group to Revise DSM-III, 1987) as well as the NINCDS-ADRDA criteria for Alzheimer’s disease (McKhann et al., 1984). Exclusion criteria were significant systemic illness making it difficult to participate and significant alcohol abuse. To compare the pathology patterns in sporadic Alzheimer’s disease with those in autosomal-dominant early-onset Alzheimer’s disease, we finally included data from one prodromal patient harbouring a Met146Ile and one established Alzheimer’s disease patient with a Thr116Asn presenilin 1 (PSEN1) mutation (see also Smith et al., 2016).

Amyloid-β positivity (amyloid-β+) was established according to a previously published approach based on 18F-flutemetamol PET evidence of global cortical amyloid-β pathology indicative of Alzheimer’s disease (Palmqvist et al., 2016). In brief, global 18F-flutemetamol standardized uptake value...
ratios (SUVR) had been calculated using a composite cortical region of interest and a whole cerebellum, the pons/brainstem region, and eroded cortical white matter composite reference region; a cut-off of SUVR ≥ 0.79 to describe amyloid-β positivity was derived using mixture modelling analysis in a large BioFINDER cohort (n = 406). In accordance with previous studies, the distribution and extent of amyloid pathology did not differ between early-onset and late-onset Alzheimer’s disease patients (Supplementary Fig. 1 and Supplementary material).

All participants gave written informed consent to participate in the study. Ethical approval was given by the Regional Ethical Committee of Lund University, Lund, Sweden and all the methods were carried out in accordance with the approved guidelines. Approval for PET imaging was obtained from the Swedish Medicines and Products Agency and the local Radiation Safety Committee at Skåne University Hospital, Sweden.

**Image acquisition**

Structural MRI was conducted on a Siemens Tim Trio 3 T scanner (Siemens Medical Solutions). High resolution T1-weighted anatomical magnetization-prepared rapid gradient echo (MPRAGE) images (repetition time = 1950 ms, echo time = 3.4 ms, 1 mm isotropic voxels and 176 slices) were acquired for volumetric analysis and PET image co-registration and template normalization. 18F-AV-1451 was synthesized at Skåne University Hospital, Lund, as described previously (Hahn et al., 2017). PET scans were performed on a GE Discovery 690 PET scanner (General Electric Medical Systems) as dynamic scans using LIST-mode 80–120 min after a bolus injection of 370 MBq of 18F-AV-1451. Low-dose CT scans for attenuation correction were performed in the same patient position immediately prior to the PET scans. PET data were reconstructed into 5 min frames using an iterative Vue Point HD algorithm with six subsets, 18 iterations with 3 mm filter, and no time-of-flight correction. The dynamic scans were motion corrected using Analysis of Functional NeuroImages (AFNI) 3dvolreg (https://afni.nimh.nih.gov) (Cox, 2012), time-averaged, and rigidly coregistered to the respective skull-stripped MRI scan.

**Image preprocessing**

All magnetic images were normalized to a common MNI152 space for further use in the PET processing pipeline. Cortical reconstruction and volumetric segmentation and parcellation were performed using FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/) (Fischl et al., 2004). Voxel-based morphometry (VBM) as implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm) was used to evaluate grey matter intensity differences as a measure of grey matter atrophy. In preparation, all individual T1-weighted magnetic resonance images were segmented into tissue classes, and the grey matter segmentations subsequently warped into a common MNI152 standard space (using a cohort-specific template created with the DARTEL toolbox and Jacobian-scaling to estimate grey matter intensity) (Ashburner and Friston, 2000). The resulting maps were smoothed with an 8 mm full-width at half-maximum Gaussian kernel. VBM analyses were adjusted for intracranial volume.

### 18F-AV-1451 PET image processing

Partial volume error correction was performed using the geometric transfer method as described in Rousset et al. (1998) using the FreeSurfer parcellations, smoothed with 5 mm full-width at half-maximum to calculate transfers across region of interest borders. The FreeSurfer parcellations in magnetic resonance space were then applied to the processed, co-registered, and time-averaged PET image to extract regional AV-1451 uptake values. Standardized uptake value (SUV) images were subsequently created based on mean uptake over 80–120 min post-injection and normalized to uptake in a grey matter masked cerebellum reference region to create voxelwise SUV images in each participant’s MRI native space (Hahn et al., 2017). All AV-1451 PET images were further warped into the common MNI152 space by using transformation measures from warping the co-registered MRI scans to the 2 mm FSL MNI152 template (http://www.fmrib.ox.ac.uk/fsl) and smoothed with 8 mm full-width at half-maximum prior to analysis.

### Statistical analyses

We performed both region of interest-based and voxelwise analyses using the 18F-AV-1451 image and the VBM-derived data. For regional analyses, we restricted statistics to three a priori defined regions of interest based on the Braak staging approach for tau pathology (Braak and Braak, 1991), which grades tau pathology into an early entorhinal (Braak I/II), a limbic (Braak III/IV), and a late neocortical (Braak V/VI) stage. We used a previously described protocol to aggregate weighted FreeSurfer regions of interest into approximative Braak stage regions of interest I/II, III/IV, and V/VI (for definitions see Supplementary Table 1) (Schöll et al., 2016). First, we tested for differences in Braak region of interest 18F-AV-1451 uptake between the different diagnostic groups using Kruskal-Wallis H-test followed by pairwise Mann-Whitney U-tests, corrected for multiple comparisons within each Braak region of interest. Group differences between healthy controls and early-onset Alzheimer’s disease or late-onset Alzheimer’s disease, respectively, were further tested voxelwise using analysis of covariance (ANCOVA) (covariates age, sex, and education), and differences between early-onset Alzheimer’s disease and late-onset Alzheimer’s disease using a two-sample t-test (covariates sex, education, and disease duration) as implemented in SPM12. Prodromal Alzheimer’s disease patients were not included in voxelwise analyses of group differences due to the small size of the early-onset promodromal Alzheimer’s disease sample.

We then explored the relationship of age at symptom onset with Braak region of interest 18F-AV-1451 retention using Spearman’s rank correlation. Associations between age at symptom onset and 18F-AV-1451 uptake were further analysed using voxelwise SPM12 multiple regression models including sex and education as covariates.

Finally, we tested voxelwise group differences in grey matter intensity between healthy controls, early-onset Alzheimer’s disease, and late-onset Alzheimer’s disease subjects using the VBM data described above. We used ANCOVA or two-sample t-test in SPM12 with sex, education, and intracranial volume or sex, education, disease duration, and intracranial volume, respectively, as covariates.
Results

Participants

All demographic information is presented in Table 1. By design, established and prodromal Alzheimer’s disease cases with late-onset of cognitive symptoms (late-onset Alzheimer’s disease and late onset prodromal Alzheimer’s disease) were older than cases with early-onset of symptoms (early-onset Alzheimer’s disease and early-onset prodromal Alzheimer’s disease), respectively. No statistically significant difference was observed for years of education or disease duration between any of the patient groups. Forty-three per cent of the control subjects were amyloid-β-positive according to their 18F-flutemetamol SUVR, and all patients with Alzheimer’s disease were amyloid-β-positive. The early-onset Alzheimer’s disease and early-onset prodromal Alzheimer’s disease subjects performed worse on the Alzheimer’s Quick Test (AQT), a test for processing speed, while the late-onset Alzheimer’s disease and late onset prodromal Alzheimer’s disease patients performed worse on the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-cog) delayed memory recall test than all other participants.

18F-AV-1451 uptake patterns in early- and late-onset Alzheimer’s disease

While the early-onset Alzheimer’s disease group revealed higher uptake in most of the temporal, lateral parietal, lateral occipital, and dorsal frontal cortical regions, sparing the primary sensory and motor cortices, regions of higher ligand retention in late-onset Alzheimer’s disease were confined to the temporal lobes and lateral parieto-occipital regions with highest uptake in the medial temporal lobe when compared to healthy controls (Fig. 1A; P < 0.05, family-wise error corrected). When compared against each other, the early-onset Alzheimer’s disease group exhibited greater uptake than late-onset Alzheimer’s disease in dorsolateral prefrontal and premotor cortex, as well as in the inferior parietal lobule (P < 0.001, uncorrected for multiple comparisons). The reverse contrast did not yield significant group differences.

Region of interest-based analyses demonstrated that 18F-AV-1451 uptake was significantly higher in all Braak regions of interest when comparing the patient groups with the healthy controls (all P < 0.001; Fig. 2A; see Supplementary material for detailed statistics). Patients with early-onset Alzheimer’s disease showed higher ligand retention than the late-onset group in the neocortical Braak regions of interest V/VI (P = 0.002), but not in the medial temporal Braak region of interest III, and only at trend level in limbic region of interest III/IV (P = 0.06), confirming the results of the voxelwise analyses. A similar pattern was observed when comparing early onset prodromal Alzheimer’s disease to late onset prodromal Alzheimer’s disease subjects (Fig. 2A), although the early onset prodromal Alzheimer’s disease group showed higher retention also in Braak region of interest III/IV (P < 0.01).

18F-AV-1451 scans of two symptomatic carriers of a PSEN1 mutation are shown in Fig. 3 to illustrate the strong resemblance with the pattern observed in sporadic early-onset Alzheimer’s disease subjects.

Effect of age on 18F-AV-1451 uptake

Figure 2B–G demonstrates the region of interest-based and voxelwise associations of age (at symptom onset for patient groups; at PET scan for healthy controls) and 18F-AV-1451 uptake in the control subjects as well as in all Alzheimer’s disease and prodromal Alzheimer’s disease patients. In
cognitively healthy elderly subjects, higher age was associated with higher $^{18}$F-AV-1451 uptake predominantly in medial temporal lobe (Figs. 2B and E; $P = 0.05$ and $P < 0.01$, uncorrected, respectively). However, in both prodromal Alzheimer’s disease (Fig. 2C) and patients with established Alzheimer’s disease (Fig. 2D), lower age was related to higher ligand retention in regions that corresponded to Braak regions of interest III/IV and V/VI, respectively. Voxelwise multiple regression of age on $^{18}$F-AV-1451 confirmed this anatomical pattern ($P < 0.001$, uncorrected; Figs. 2F and G).

$^{18}$F-AV-1451 uptake and grey matter atrophy

Grey matter atrophy was present in both the early-onset Alzheimer’s disease and in late-onset Alzheimer’s disease subjects when compared with healthy controls ($P < 0.001$, uncorrected), while direct comparison of the patient groups yielded no significant differences (Fig. 1B). Contrast maps against controls indicated cortical involvement of $^{18}$F-AV-1451 uptake was more widespread than grey matter atrophy, while the only atrophic regions without elevated $^{18}$F-AV-1451 uptake were deep nuclei, e.g. the thalamus and basal ganglia (Fig. 1B).

Discussion

The aim of the present study was to examine whether the extent and distribution of tau pathology (measured with $^{18}$F-AV-1451 PET) differed between early-onset and late-onset Alzheimer’s disease patients. We found that patients with early-onset Alzheimer’s disease were more prone to tau aggregation in widespread neocortical regions, while the medial temporal lobe showed peak $^{18}$F-AV-1451 uptake in late-onset Alzheimer’s disease. Additionally, we showed that two very young subjects (aged 40 and 44 years) with a PSEN1 mutation showed wide involvement of the neocortex with relative sparing of the medial temporal lobe, a pattern akin to the early-onset Alzheimer’s disease group. These preliminary findings indicate that age is an important contributor to Alzheimer’s disease heterogeneity and highlight the potential of tau PET for capturing phenotypic variation across Alzheimer’s disease patients.

The observed greater extent and neocortical-predominant pattern of tau pathology in early-onset compared to late-
Figure 2. $^{18}$F-AV-1451 uptake in Braak regions of interest and effect of continuous age on $^{18}$F-AV-1451 uptake. (A) Box plots displaying $^{18}$F-AV-1451 uptake in regions of interest approximating Braak stages of tau pathology. All patient groups had higher uptake than the controls in each region of interest (all $P < 0.001$). (B–D) Scatter plots displaying the relationship between age at symptom onset (for established and prodromal Alzheimer’s disease patients, age at PET examination for healthy controls) and $^{18}$F-AV-1451 uptake in Braak regions of interest. (E–G) Voxelwise multiple regressions of continuous age (at symptom onset for patients, at PET examination for healthy controls) on $^{18}$F-AV-1451 uptake. Higher age showed a tendency to be associated with higher $^{18}$F-AV-1451 uptake predominantly in medial temporal lobe ($P < 0.01$, uncorrected) (E), while lower age was associated with higher ligand uptake in regions corresponding to Braak regions of interest III/IV (prodromal Alzheimer’s disease, pAD) (F) and Braak III-VI (Alzheimer’s disease, AD) (G). EOAD = early-onset Alzheimer’s disease; EOOpAD = early-onset prodromal Alzheimer’s disease; LOAD = late-onset Alzheimer’s disease; LOpAD = late-onset prodromal Alzheimer’s disease; HC = healthy controls; ROI = region of interest.
onset Alzheimer’s disease is in line with previous neuro-pathological, structural MRI, and 18F-AV-1451 studies. (Frisoni et al., 2007; Rabinovici et al., 2010; Ossenkoppele et al., 2016). Although it could be perceived as counterintuitive since late-onset Alzheimer’s disease patients have more time to accumulate tau pathology during their lifes, there are several possible explanations for why greater tau load is required in early-onset Alzheimer’s disease patients before cognitive impairment becomes apparent. First, patients with late-onset Alzheimer’s disease more often harbour comorbid pathologies (e.g. vascular damage, TDP-43, α-synuclein) (Barkhof et al., 2007; Serrano-Pozo et al., 2014) that in synergy with amyloid-β and tau may induce cognitive deficits, something we did not have the means to explore in this study. Second, patients with early-onset Alzheimer’s disease more often have cognitive reserve that enables them to better preserve cognition in the face of similar pathological burden (Stern, 2012). Third, the molecular synergy between amyloid-β and tau might change during the life span, resulting in distinct regional neuronal vulnerability as a function of age. Finally, distinct disease pathways might hypothetically be involved in early-onset and late-onset Alzheimer’s disease, which ultimately result in differential neurodegenerative patterns at different ages. Several limitations should be considered when interpreting our results. The prodromal Alzheimer’s disease patient group was very small. Although the age effect pointed in similar directions as in the established dementia group, future studies with larger sample sizes are needed to determine whether topographical differences can already be appreciated at the pre-dementia stage. Moreover, the lack of significant difference in grey matter atrophy when comparing early-onset Alzheimer’s disease and late-onset Alzheimer’s disease was surprising given that this has been established in several previous studies and that we did notice distinct 18F-AV-1451 patterns at a similar statistical threshold. This may also partly be attributed to the small samples. Alternatively, it could be hypothesized that tau pathology is spreading throughout the brain with atrophy following the topography of tau with a temporal delay. In this sample of relatively mildly affected individuals, 18F-AV-1451 may be more sensitive than structural MRI for detecting early brain changes, which can formally be tested in future longitudinal studies. Furthermore, albeit using the conventional cut-off of 65 years at age-of-onset, this
represents a highly arbitrary number. To circumvent potential bias due to the chosen threshold, we also performed regression analyses using age as a continuous variable obtaining similar results as in the dichotomized analyses (Fig. 2B–G). Finally, 18F-AV-1451 imaging is still in its early days, and we did not obtain sufficient control data to enable proper age-matching with the respective patient groups. The proportion of amyloid-positive individuals was furthermore above what has been reported earlier in healthy controls of that age (Jansen et al., 2015), which might have affected our results from comparing patients with Alzheimer’s disease and controls in that more than exclusively age-related tau pathology might be present in our controls that in turn might represent a sample of preclinical Alzheimer’s disease (Scholl et al., 2016). Lastly, the voxelwise comparison of early-onset and late-onset Alzheimer’s disease only yielded significantly different clusters at an uncorrected $P$-level of 0.001, uncorrected for false-positive discoveries.

While topographical distributions of 18F-AV-1451 uptake clearly diverged with age-at-onset, 18F-AV-1451 uptake in the inferior and medial temporal cortex was the common denominator in which both early-onset and late-onset Alzheimer’s disease differed from healthy controls. This might prove useful when applying the recently proposed A/T/N classification system (Jack et al., 2016). In addition to ‘A’ (amyloid-β pathology) and ‘N’ (neurodegeneration, i.e. hippocampal volume, Alzheimer’s disease specific glucose hypometabolism, CSF total tau) in the previous classification system, ‘T’ has now been incorporated to represent the unique contribution of tau pathology. Our findings suggest that the inferior and medial temporal cortex may be the most optimal regions of interest to yield maximum diagnostic accuracy across the wide clinical spectrum of Alzheimer’s disease.

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**Conflict of interest**

Drs Schöll, Ossenkoppele, Palmqvist, Strandberg, Ohlsson, Jögi, and Smith report no disclosures. Dr Hansson has served at advisory boards Eli Lilly, and received research support from GE Healthcare and Hoffmann La-Roche.

**Supplementary material**

Supplementary material is available at *Brain* online.

**References**


