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ORIGINAL ARTICLE

Level of education mitigates the impact of tau pathology on neuronal function

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Abstract

Purpose Using PET imaging in a group of patients with Alzheimer's disease (AD), we investigated whether level of education, a proxy for resilience, mitigates the harmful impact of tau pathology on neuronal function.

Methods We included 38 patients with mild-to-moderate AD (mean age 67 ± 7 years, mean MMSE score 24 ± 4, mean years of education 14 ± 4; 20 men, 18 women) in whom a [^{18}F]AV-1451 scan (a measure of tau pathology) and an [^{18}F]FDG scan (a measure of neuronal function) were available. The preprocessed PET scans were *z*-transformed using templates for [^{18}F]AV-1451 and [^{18}F]FDG from healthy controls, and subsequently thresholded at a *z*-score of ≥3.0, representing an one-tailed *p* value of 0.001. Next, three volumes were computed in each patient: the tau-specific volume (tau pathology without neuronal dysfunction), the FDG-specific volume (neuronal dysfunction without tau pathology), and the overlap volume (tau pathology and neuronal dysfunction). Mean *z*-scores and volumes were extracted and used as dependent variables in regression analysis with years of education as predictor, and age and MMSE score as covariates.

Results Years of education were positively associated with tau-specific volume ($\beta = 0.362$, $p = 0.022$), suggesting a lower impact of tau pathology on neuronal function in patients with higher levels of education. Concomitantly, level of education was positively related to tau burden in the overlap volume ($\beta = 0.303$, $p = 0.036$) implying that with higher levels of education more tau pathology is necessary to induce neuronal dysfunction.

Conclusion In patients with higher levels of education, tau pathology is less paralleled by regional and remote neuronal dysfunction. The data suggest that early life-time factors such as level of education support resilience mechanisms, which ameliorate AD-related effects later in life.

Keywords Glucose metabolism · Brain reserve · Brain maintenance · Resilience · [^{18}F]AV-1451 · [^{18}F]FDG

Introduction

The neuropathological hallmarks of Alzheimer's disease (AD), beta-amyloid (Aβ) plaques and neurofibrillary tangles, appear to evolve in temporal order with Aβ becoming abnormal first, followed by tau pathology and subsequently neuronal injury [1]. During these pathophysiological processes, tau pathology, in contrast to Aβ pathology, is more closely associated with neuronal dysfunction [2, 3] and symptom severity [4, 5] in individuals with typical AD and variants of AD such as posterior cortical atrophy, the logopenic variant and the behavioural variant [2, 6, 7].

While the direct relationship between tau pathology and neuronal injury in space and time is now better understood, substantial heterogeneity in clinical severity in individuals with comparable degrees of pathology remains a puzzling feature. To accommodate this heterogeneity, resilience-related concepts such as cognitive reserve, brain reserve (BR) and brain maintenance (BM) have been introduced,

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and have been suggested to weaken the relationship between AD-related pathophysiology and symptom severity. Cognitive reserve refers to the adaptability of cognitive processes to maintain functionality and BR accounts for differences in brain integrity [8, 9]. In turn, the concept of BM is associated with neuroprotective mechanisms supporting the preservation of brain integrity [10, 11].

Consistent with these concepts, we recently showed that patients with typical AD with higher levels of education are able to tolerate more severe and spatially extended tau pathology than AD patients with lower levels of education but similar cognitive impairment [12]. One possible explanation for this finding is that the impact of tau pathology on neuronal function is less harmful in patients with higher levels of education due to mechanisms associated with BR and BM. These mechanisms potentially support resilience to brain pathology [13] by, for example, boosting neuronal plasticity through the upregulation of neuronal growth factors.

To investigate these possibilities, we used a novel volume-based PET imaging approach to assess whether a resilience-related proxy, namely education, affects the association between tau pathology (i.e. [^{18}F]AV-1451 PET) and neuronal dysfunction (i.e. [^{18}F]FDG PET) in patients with typical AD and variants of AD. In each patient, we extracted three distinct volumes: (1) the tau-specific volume (all regions showing only significant tau pathology in the absence of neuronal dysfunction); (2) the FDG-specific volume (all regions showing significant neuronal dysfunction in the absence of tau pathology); and (3) the overlap volume (all regions showing significant tau pathology load and neuronal dysfunction). Assuming that level of education mitigates the effects of tau pathology on glucose metabolism, we hypothesized the following: (1) the tau-specific volume is larger despite relative preservation of regional glucose metabolism in individuals with higher levels of education; (2) the mean tau pathology load in the overlap volume is positively correlated with years of education; and (3) irrespective of level of education, the volume of reduced glucose metabolism is smaller than the tau volume given the presumed temporal evolution of AD biomarkers [14].

Materials and methods

Participants

The study group comprised 38 patients with mild-to-moderate AD recruited from the interdisciplinary memory centres of the University Hospital Cologne and the University Hospital Bonn. The patients were diagnosed with probable AD dementia using the recommended NIA-AA criteria [15] including diagnostic amyloid PET imaging or CSF measurements. All participants underwent a PET scan with [^{18}F]AV-1451 for the in-vivo assessment of tau pathology and a PET scan with [^{18}F]FDG for the evaluation of neuronal dysfunction at the Department of Nuclear Medicine of the University Hospital Cologne. All participants provided signed informed consent regarding the scientific evaluation and publication of their data.

PET acquisition

PET scans were performed on a Siemens Biograph mCT Flow 128 Edge scanner (Siemens, Knoxville, TN) and were iteratively reconstructed using a 3-D OSEM algorithm (four iterations, 12 subsets, gaussian filter, 5 mm full-width at half-maximum, matrix 128 × 128, slice thickness 3 mm). The two PET scans were acquired no more than 3 months and on average less than 1 month apart. Administration parameters are summarized in Table 1.

PET image processing

In each individual, the [^{18}F]AV-1451 scan was coregistered to the [^{18}F]FDG scan using SPM12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK). The coregistered [^{18}F]AV-1451 scan and the native [^{18}F]FDG scan were then normalized to a [^{18}F]FDG PET template in MNI space [16]. Using in-house scripts in MATLAB R2016a (The MathWorks, Inc., Natick, MA, USA), the normalized scans were intensity-standardized to the whole cerebellum, which was used as the reference region. The preprocessed images were then *z*-transformed

Table 1 Descriptive characteristics

Characteristic	Value
Number of patients	38
Men	20
Women	18
Age (years), mean (SD)	67.11 (6.97)
MMSE score, mean (SD)	23.87 (4.45)
Years of education, mean (SD)	13.85 (3.92)
[^{18}F]AV-1451, mean (SD)	
Dose (MBq)	236.26 (48.11)
Administration time after injection (min)	94.81 (26.87)
[^{18}F]FDG, mean (SD)	
Dose (MBq)	216.92 (49.22)
Administration time after injection (min)	36.24 (10.55)

SD standard deviation, *MMSE* Mini Mental State Examination

using an [^{18}F]AV-1451 PET template and an [^{18}F]FDG PET template from a healthy control sample ($n = 15$, mean age at FDG scan 67.47 years, mean MMSE score at FDG scan 28.87, mean years of education 16.67) acquired at two different time points and provided by the Alzheimer's Disease Neuroimaging Initiative database (http://adni.loni.usc.edu/). The control sample was age-matched to our AD sample. Numerically, the mean years of education in the healthy control sample was slightly higher than in the patient sample, most likely reflecting differences in the German and North American educational systems ($U = 148$, $p = 0.007$). For further information on the processing of the healthy control templates see the Supplementary material.

The z-transformed images were thresholded at a z-score of ≥3.0 approximately corresponding to an one-tailed p value of 0.001. In a next step, using a batch script employing the imcalc function implemented in SPM12, three volumes were extracted: (1) the tau-specific volume comprising regions characterized by significant tau pathology but no significant change in glucose metabolism; (2) the FDG-specific volume comprising regions with significant changes in glucose metabolism in the absence of tau pathology; and (3) the overlap volume comprising regions in which both the [^{18}F]AV-1451 and the [^{18}F]FDG scan showed a z-score of ≥3.0. The difference between the tau-specific volume and the FDG-specific volume was also extracted. A positive difference value indicated a larger tau-specific volume than FDG-specific volume, whereas a negative value indicated the reverse. All computed volumes, the volume difference and z-scores of the volumes were then used for further statistical analysis.

To ensure that the results were not predominantly driven by the predefined z-score threshold of ≥3.0, the same analysis was performed with the PET scans thresholded at a more liberal z-score of ≥2.0, representing an one-tailed p value of 0.02. A subanalysis ($z \geq 3.0$) was also performed limiting the dataset to data from patients with typical AD to ensure that the results were not solely driven by the data from patients with variants of AD.

Statistical analysis

Multivariable regression analysis was performed with SPSS version 21 (IBM Corp., Armonk, NY USA). Years of education (that is, schooling and subsequent professional education including vocational or university training) was employed as the predictor with the volumes, mean z-scores within these volumes and the difference in volume as dependent variables, controlling for age and MMSE score. The models were further tested for a potential gender effect. As the gender effect was not significant, it was excluded from the final analysis. Moreover, one-tailed bivariate correlation analysis was performed to evaluate the association between the mean z-scores of the respective volumes. The significance threshold for all analyses was set at $p < 0.05$.

The graphs of the results were computed using R (R: A language and environment for statistical computing, 2018; R Core Team, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). The brain surface illustrations were created using the CAT12 toolbox implemented in SPM and the Surf Ice toolbox (https://www.nitrc.org/projects/surfice/).

Results

Descriptive data

Of the 38 patients, 26 were diagnosed with typical AD, six with the logopenic variant, three with posterior cortical atrophy, two with the behavioural variant, and one with atypical AD without further specification. The patients with lower levels of education had on average 11 years of education, whereas the patients with higher levels of education level had on average ≥18 years of education (see Supplementary material for information on the German education system). Descriptive data of the group are presented in Table 1. One extreme outlier was removed from the analysis to fulfil the underlying assumptions for regression analysis.

Associations with level of education

A significant positive association was observed between years of education and tau-specific volume ($\beta = 0.362$, $t = 2.414$, $p = 0.022$). In other words, higher levels of education were associated with more brain areas showing preserved metabolism despite the presence of tau pathology. Furthermore, in regions with tau pathology and hypometabolism overlap, years of education was positively correlated with tau pathology load ($\beta = 0.303$, $t = 2.183$, $p = 0.036$), but not with the degree of hypometabolism ($\beta = -0.057$, $t = -0.385$, $p = 0.703$). Moreover, no significant effect was observed in the regression analysis between level of education and FDG-specific volume ($\beta = -0.242$, $t = -1.423$, $p = 0.164$). Furthermore, a significant positive relationship was observed between years of education and the difference between the tau-specific volume and the FDG-specific volume ($\beta = 0.342$, $t = 2.190$, $p = 0.036$). The difference values were not exclusively positive, meaning that in patients with the lowest levels of education the FDG-specific volume was even larger than the tau-specific volume.

Table 2 Results of regression analysis

	t	*β*	*P*	95% CI	*F*	df	*p*	Adjusted R^2
Tau-specific volume					5.306	3,33	0.004	0.264
Level of education	2.414	0.362	0.022	0.002, 0.025				
MMSE score	−1.903	−0.293	0.066	−0.021, 0.001				
Age	−2.558	−0.376	0.015	−0.014, −0.002				
Mean tau burden in overlap volume (tau-specific/FDG-specific overlap)					8.109	3,33	<0.001	0.372
Level of education	2.183	0.303	0.036	0.016, 0.465				
MMSE score	−2.835	−0.403	0.008	−0.511, −0.084				
Age	−3.150	−0.428	0.003	−0.317, −0.068				
FDG-specific volume					1.704	3,33	0.185	0.055
Level of education	−1.423	−0.242	0.164	−0.016, 0.003				
MMSE score	1.827	0.319	0.077	−0.001, 0.017				
Age	0.595	0.099	0.556	−0.004,0.007				
Volume difference (tau-specific – FDG-specific)					4.061	3,33	0.015	0.203
Level of education	2.190	0.342	0.036	0.001, 0.039				
MMSE score	−2.086	−0.334	0.045	−0.037, 0.000				
Age	−1.855	−0.284	0.072	−0.020, 0.001				

The table includes the statistical model summaries of all regression analyses

CI confidence interval, *df* degrees of freedom, *MMSE* Mini Mental State Examination

The results of the regression analysis are summarized in Table 2 and respective plots are shown in Fig. 1 and Supplementary Fig. 1a. Figure 2 illustrates a brain projection showing the increase in tau-specific volume with increasing years of education.

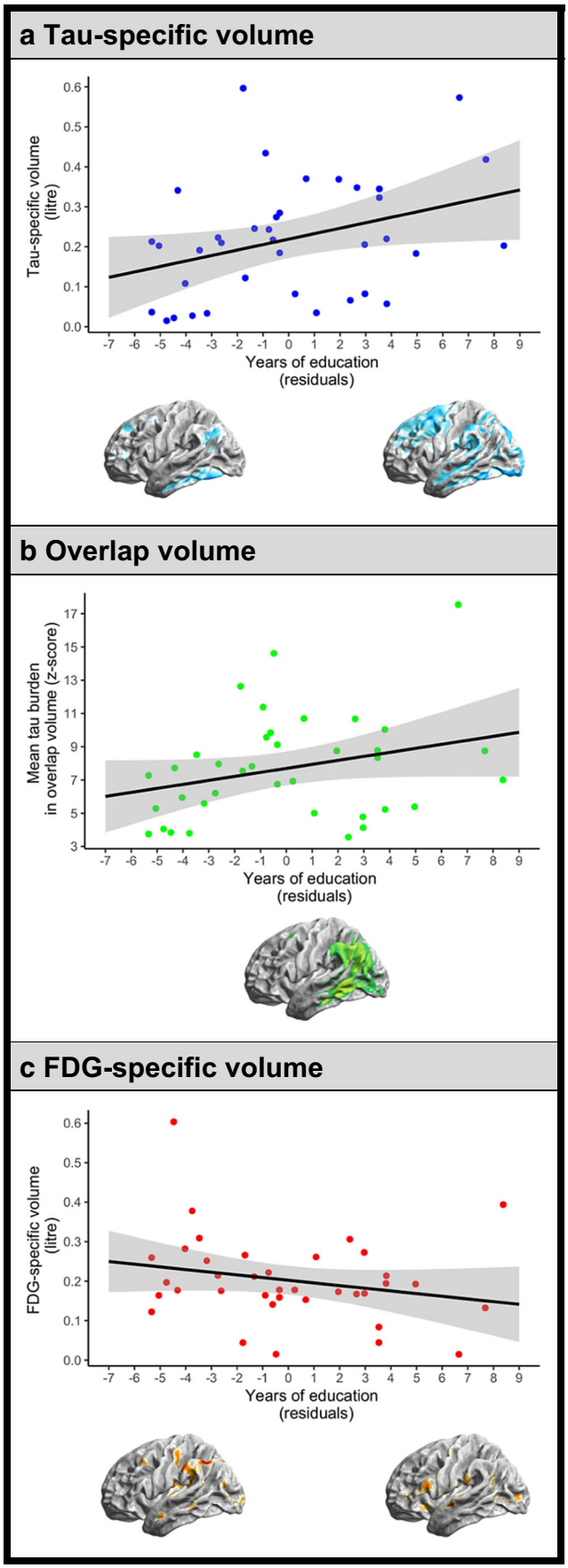
Aside from this, a positive trend for an association was found between the respective average *z*-scores for hypometabolism and tau pathology within the overlap volume ($r = 0.264$, $p = 0.057$; Supplementary Fig. 1b). In contrast, the average *z*-scores of the FDG-specific volume were not correlated with the average *z*-scores of the tau-specific volume ($r = -0.109$, $p = 0.260$; Supplementary Fig. 1c). Moreover, the subanalysis including only patients with typical AD showed a trend for significance of the main variables of interest (Supplementary Table 1). In addition, the confirmatory analysis using a threshold *z*-score of ≥2.0 yielded similar results, supporting our approach (Supplementary Table 2).

Discussion

Several studies using PET imaging have shown that the spatial extent of tau pathology is closely related to changes in glucose metabolism, a measure of neuronal dysfunction. Here, we report evidence that level of education mitigates the local impact of tau pathology on neuronal function. We observed that the volume of brain regions with relatively preserved metabolism despite the presence of significant tau pathology (i.e. the tau-specific volume) is greater in patients with higher levels of education. Furthermore, our data suggest that in regions characterized by coexisting tau pathology and neuronal dysfunction (i.e. the overlap volume), a greater tau burden is required to cause comparable metabolic dysfunction in individuals with higher levels of education. Taken together, our findings point towards the existence of protective mechanisms against tau pathology, which may be associated with the early life-time factor of education. We discuss below the current findings based on the concept of BR continued by an argumentation relating to resilience factors supporting BM.

An explanation based on the concept of brain reserve

Numerous studies have shown that life-time factors, such as education, play an important role in prolonging and slowing cognitive decline following the advent of brain pathology [12, 17–22]. Education, an early life-time factor, has consistently been associated with higher socioeconomic status, better health, less chronic stress and life-long mental stimulation, factors that probably contribute to better brain health later in life [23–26]. With an accumulating body of evidence across neurological conditions, it is believed that education can protect and provide resilience against the harmful effects of pathology [27]. In line with this, we found that higher levels of education are associated with less pronounced effects of tau pathology on neuronal function. Moreover, more tau pathology appears necessary to induce changes in glucose metabolism in individuals with higher levels of education.



◀ **Fig. 1** Regression analysis including years of education (residuals) corrected for MMSE and age as predictor and mean tau burden (*z*-score) and volumes (litre) as dependent variables (**a** *blue* tau-specific volume, **b** *green* mean tau burden in overlap volume, **c** *red* FDG-specific volume; *grey areas* 95% confidence intervals). Brain projections of the respective volumes are illustrated below each scatterplot. **a** and **c** show the volume extents in a patient with a low level of education (*left*) and a patient with a high level of education (*right*), and **b** depicts the average overlap volume in patients with typical AD. The respective volumes were rendered on a brain surface in MNI space using the CAT toolbox implemented in SPM12

These findings may first be explained based on the concept of BR, which accounts for the individual neurobiological capital such as neuron count and synaptic density [9]. Accordingly, individuals with a high BR will show less severe symptoms than individuals with a low BR despite similar brain pathology, because they possess more BR to counteract the brain damage. Hence, although the same numbers of neurons or synapses are rendered dysfunctional by misfolded tau aggregates in individuals with low and high levels of education, an individual with a higher level of education will be able to counteract the brain damage given that he/she possesses enough resources in the form of yet-unaffected neurons or synapses. Due to the activation of these (thus far) spared resources, the metabolic rate (i.e. FDG uptake on PET) in individuals with higher levels of education may in turn not significantly deviate from that detected in healthy controls despite tau aggregation. Furthermore, according to the BR-concept, a greater pathological burden is necessary to eventually affect the compensatory resources in individuals with higher levels of education, which may account for our finding of greater tau burden in the overlap volume in patients with higher levels of education.

Importantly, it has been postulated that glucose metabolism reflects synaptic function rather than overall neuronal function [28]. The possible BR-related compensatory process may thus be a matter rather of synaptic density and plasticity than of total neuron count. Indeed, several studies using rodent models have demonstrated that enriched environments, which are used to study the benefits of life-long cognitive stimulation, promote neuronal plasticity in the form of increased synaptic density [29–31] and dendritic branching [32, 33]. Similar effects are believed to occur in humans. With the recent development of PET tracers to visualize changes in synaptic density [34], future studies will be able to directly elucidate the protective effect of education on AD-related pathology.

Concerning our reasoning based on the BR concept, it must be emphasized that the neurotoxic effects of tau pathology on neuronal function are considered similar at different levels of education. Yet, the detectable and measurable outcome (i.e. the FDG PET signal) of regional tau pathology on neuronal function differs according to the individual extent of underlying compensatory resources. One may, however, also argue

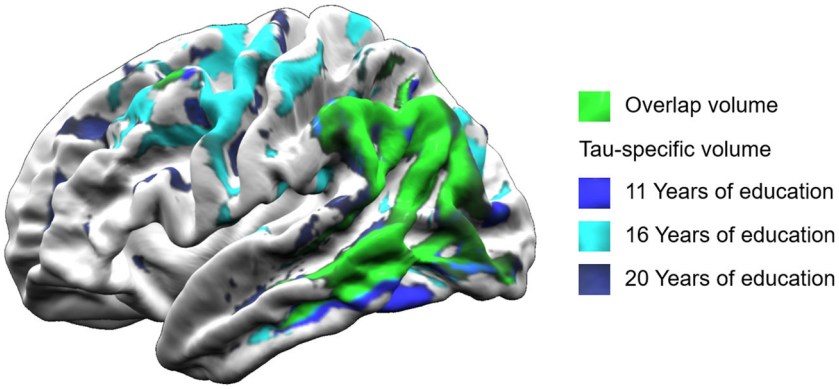


Fig. 2 Brain projection showing the tau-specific volume in relation to level of education: *green* average overlap volume (i.e. significant tau pathology and neuronal dysfunction) in patients with typical AD, *blue* average tau-specific volumes in three groups with different levels of education (average 11, 16 and 20 years) surrounding the overlap volume. Importantly, the volumes shown were derived solely from patients with typical AD, because those with atypical AD showed different topographical patterns. Moreover, the tau-specific volume in the patients with an average of 16 years of education is in addition to the volume of those with an average of 11 years of education. Likewise, the volume in the patients with an average of 20 years of education is in addition to the two volumes of the groups with less education. The respective volumes were rendered on a brain surface in MNI space using the Surf-Ice toolbox

that in individuals with higher levels of education the impact of tau pathology on neuronal function is ameliorated by resilience factors supporting BM, as discussed below.

An explanation based on resilience factors supporting brain maintenance

Again, rodent studies have provided valuable information on resilience factors that are associated with life-long engagement and facilitate clearance or decreases in tau pathology and neuroinflammation, thereby supporting maintenance of brain integrity. These factors are potentially associated with level of education in humans and thus contribute to the current findings. Given the complexity of these resilience factors, we mention, within the scope of this discussion, only a few examples that may have contributed to the current findings.

Over the past decade, several cellular growth factors have been reported to be neuroprotective, such as the brain-derived neurotrophic factor (BDNF). BDNF has been demonstrated in vitro to alter the phosphorylation of tau [35] and has consistently been found to positively affect memory processes even in subjects with dementia (for review see [36]). More recently, elevated CSF levels of vascular endothelial growth factor [37] and increased serum levels of insulin growth factor [38] have also been associated with healthier brain ageing and brain volume late in life. Aside from the upregulation of these growth factors, distinct proteomic signatures [39] and genes [40, 41] have been related to neuronal resilience. For example, increased expression of genes involved in the control of lysosomes has been found after long-term physical exercise. This upregulation appears to ameliorate the neurotoxic effects of hippocampal tau pathology in rodents [41]. Interestingly, the lysosomal pathway has been suggested to mediate the degradation of tau isoforms [42, 43].

So far, it remains unknown whether these molecular underpinnings are directly associated with early life-time factors, such as education, or whether they are more closely related to life-long cognitive and physical engagement. Longitudinal studies, including elaborate questionnaires of life-time cognitive and physical activities, are necessary to gain further insights into the relationship between early life-style factors and protective molecular signatures later in life.

Downstream effects of regional tau pathology

Despite the observation that tau pathology appears to be less harmful to neuronal function in individuals with higher levels of education, we conversely observed that changes in neuronal function in the absence of local tau pathology appear to be potentiated in individuals with lower levels of education. These changes may represent effects of neuropathology aggregation in remote but functionally connected brain regions in the sense of functional deafferentation or diaschisis.

Interestingly, molecular studies have shown that tau pathology preferentially affects long-range projection neurons rather than locally projecting neurons [44, 45]. Thus, signal changes detected on [^{18}F]FDG PET probably represent downstream projection sites from the neuron affected by tau pathology. This may cause a topographic discordance between the [^{18}F]AV-1451 and [^{18}F]FDG signals. Indeed, recently, it has been suggested that the topographic overlap between tau pathology and neuronal dysfunction becomes less coherent as the disease progresses [46]. Given these findings, it may be that the disease in individuals with lower levels of education in

our sample had already progressed to more advanced stages. Furthermore, the downstream effects of tau pathology could be more severe in patients with lower levels of education, because they do not possess sufficient compensatory or maintenance mechanisms to counteract the local upstream effects of misfolded tau aggregates. This would explain why in patients with lower levels of education the FDG-specific volumes were greater than the tau-specific volumes.

Limitations

We used a volume-based approach with a predefined threshold, which may have led to underestimation or overestimation of the overall tau pathology and hypometabolism pattern. Yet the analysis based on a more liberal threshold yielded similar results, supporting the current findings. Moreover, with the approach used, we were able to perform a group analysis including individuals with different variants of pathology distribution. However, as the patient groups with atypical AD were relatively small, we could not run subsequent analyses for each group. Moreover, the potential contribution of Aβ pathology could not be considered in the analyses as amyloid PET scans were not available in all patients. Nonetheless, all patients were amyloid-positive based on either CSF or PET imaging measures. Moreover, we cannot rule out the possibility that our findings, although less likely, were driven by a faster spatial spread of tau pathology in patients with higher levels of education. Lastly, we used an indirect proxy of neuronal resilience, namely educational attainment, as there is no direct measure available yet. It is possible that more elaborate measures of resilience such as life-long cognitive engagement, physical activity or even nutrition may be more closely associated with the observed effects. Overall, future studies in larger cohorts using elaborate questionnaires on life-time experience are required to establish direct measures of neuronal resilience.

Conclusion

The results of this study indicate that level of education is associated with resilience capacity, which ameliorates the neurotoxic effects of misfolded tau aggregates on neuronal function in AD. This finding potentially explains why AD patients with higher levels of education can tolerate more tau pathology than those with lower levels of education and similar cognitive impairment. It would be of interest to examine whether the current findings are transferrable to other tauopathies such as progressive supranuclear palsy, corticobasal syndrome and frontotemporal dementia. These tauopathies are characterized by morphological differences in tau aggregates, but the disease mechanisms appear similar, at least to some degree [47]. Thus, the elucidation of resilience mechanisms may lead to treatment interventions that are relevant not only to AD but also to other neurodegenerative diseases.

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Author's contributions M.C.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.C.H., G.N.B., A.D. and T.vanE. were involved in the conception and design of the study, analysis of the data and drafting the manuscript. E.K. was involved in the conception of the study and drafting the manuscript. Ö.A.O., J.K., F.J., K.F., G.R.F. and B.N. were involved in the acquisition of the data and drafting the manuscript.

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Compliance with ethical standards

Conflicts of interest MH, GNB, ÖAO, JK, FJ, KF, and BN have no conflict of interest. GRF received honoraria for speaking engagements from Bayer, Desitin, Ergo DKV, Forum für medizinische Fortbildung FomF GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer, and Sportärztebund NRW. EK received grants from the German Ministry of Education and Research, the German ParkinsonFonds, and the German Parkinson Society as well as honoraria from Oticon GmbH, Hamburg, Germany; Lilly Pharma GmbH, Bad Homburg, Germany; Bernafon AG, Bern, Switzerland; Desitin GmbH, Hamburg, Germany. AD reports having received consulting and speaker honoraria as well as research support from Siemens Healthcare, AVID Radiopharmaceuticals, Lilly, Piramal (now Life Molecular Imaging) and GE Healthcare. TvE reports having received consulting and speaker honoraria as well as research support from Siemens Healthcare, AVID Radiopharmaceuticals, Lilly, Shire Germany, Piramal (now Life Molecular Imaging) and GE Healthcare. Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the University Cologne and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

Informed consent Informed consent was obtained from all individual participants included in this research project as part of the study for the scientific evaluation of the AV-1451 tracer.

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