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RESEARCH ARTICLE

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Tau as a biomarker of cognitive impairment and neuropsychiatric symptom in Alzheimer's disease

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Abstract

The A/T/N research framework has been proposed for the diagnosis and prognosis of Alzheimer's disease (AD). However, the spatial distribution of ATN biomarkers and their relationship with cognitive impairment and neuropsychiatric symptoms (NPS) need further clarification in patients with AD. We scanned 83 AD patients and 38 cognitively normal controls who independently completed the mini-mental state examination and Neuropsychiatric Inventory scales. Tau, Aβ, and hypometabolism spatial patterns were characterized using Statistical Parametric Mapping together with [18F]flortaucipir, [18F]florbetapir, and [18F]FDG positron emission tomography. Piecewise linear regression, two-sample *t*-tests, and support vector machine algorithms were used to explore the relationship between tau, Aβ, and hypometabolism and cognition, NPS, and AD diagnosis. The results showed that regions with tau deposition are region-specific and mainly occurred in inferior temporal lobes in AD, which extensively overlaps with the hypometabolic regions. While the deposition regions of Aβ were unique and the regions affected by hypometabolism were widely distributed. Unlike Aβ, tau and hypometabolism build up monotonically with increasing cognitive impairment in the late stages of AD. In addition, NPS in AD were associated with tau deposition closely, followed by hypometabolism, but not with Aβ. Finally, hypometabolism and tau had higher accuracy in differentiating the AD patients from controls (accuracy = 0.88, accuracy = 0.85) than Aβ (accuracy = 0.81), and the combined three were the highest (accuracy = 0.95). These findings suggest tau pathology is superior over Aβ and glucose metabolism to identify cognitive impairment and NPS. Its results support tau accumulation can be used as a biomarker of clinical impairment in AD.

KEYWORDS
Alzheimer's disease, amyloid-β, cognitive impairment, hypometabolism, neuropsychiatric symptoms, tau

Mingxi Dang and Qian Chen contributed equally to this study.

1 | INTRODUCTION

Amyloid-β (Aβ), tau, and hypometabolism are typical biomarkers for Alzheimer's disease (AD; Bensamoun et al., 2015), and are used as a critical part for the diagnosis of AD (Dubois et al., 2014; Jack Jr. et al., 2018; Sperling et al., 2011). Recent evidence suggests that although Aβ plaques play a key role in AD pathogenesis, the spatial appearance, progression, and absolute amount of tau tangles are more correlated to dementia and cognition impairment than amyloid plaques (Morris et al., 2018; Nelson et al., 2012). Several longitudinal studies found tau to be a promising tool for predicting cognitive change, superior to Aβ, structural magnetic resonance imaging (MRI), cerebrospinal fluid biomarkers, or hypometabolism (Aschenbrenner et al., 2018; Chiotis et al., 2021; Lagarde et al., 2022; Ossenkoppele et al., 2021). Tau pathology has also been observed to be closely associated with AD-related hypometabolism, and they are strongly co-localized in the posterior cingulate and parietotemporal regions (Iaccarino et al., 2021; Okamura et al., 2014; Ossenkoppele et al., 2016; Ossenkoppele et al., 2018). Therefore, tau is suspected to be essential for the clinical impairment in AD and it may be the key to understanding the cognitive decline and neuropsychiatric symptoms (NPS) of AD to explore the brain spatial lesion patterns of different pathological biomarkers.

NPS are core features of AD, and almost all people diagnosed with AD develop NPS at some stage during their disease progress. These symptoms adversely reduce the quality of life of patients and caregivers, as well as being associated with more rapid progression to severe dementia and earlier death (Teng et al. 2007; Fischer et al., 2012; Nunes et al., 2019; Shin et al., 2005). Although molecular imaging studies of NPS are very limited, the available findings indicated that NPS could increase the burden of tau (Marshall et al., 2006; Tekin et al., 2001) and Aβ accumulation (Johansson et al., 2020; Mori et al., 2014), as well as reduce the metabolic rate (Ng et al., 2017). A recent study found that tau was primarily associated with NPS, rather than Aβ or neurodegeneration using voxel-based morphometry images, in normal elderly, mild cognitive impairment, and AD (Tissot et al., 2021). To elucidate the pathological mechanism of NPS in AD, it is necessary to investigate the relationship between NPS and different molecular image markers in AD patients with ATN image data.

In addition, effectively and accurately distinguishing patients with AD from cognitively normal controls (NC) is a major challenge in clinical diagnosis. Undoubtedly, positron emission tomography (PET) techniques using multi-tracers have the potential to greatly improve the clinical diagnostic accuracy of AD (Foster et al., 2007; Mattsson et al., 2014; Ossenkoppele et al., 2018). However, it is not clear which imaging biomarker or combination of these biomarkers is better at differentiating AD patients from healthy elderly individuals. Therefore, it is necessary to compare the discriminative accuracy of these different molecular imaging markers and evaluate whether the classification accuracy is improved when multimodal molecular imaging biomarkers are used together.

Overall, more research data are needed to clarify the relationship between different pathological biomarkers and clinical impairment of AD. We, therefore, used the tau PET tracer [^{18}F]flortaucipir together with Aβ PET and glucose metabolism PET in healthy elderly controls and AD patients, to (1) characterize the changes of tau accumulation, Aβ deposition, and glucose hypometabolism with cognitive decline; (2) assess the relationship between NPS and different imaging biomarkers; and (3) investigate the potential powers of tau, Aβ, hypometabolism, and their combinations for the clinical diagnosis of AD. We hypothesized that tau pathology would be superior over Aβ and glucose metabolism to identify AD, cognitive impairment, and NPS. In addition, Aβ and glucose metabolism would provide some complementary information about the clinical diagnosis of AD.

2 | MATERIALS AND METHODS

2.1 | Participants

The participants in the present study were recruited from the Beijing Aging Brain Rejuvenation Initiative (BABRI) project. BABRI is an ongoing community-based cohort study in China, which focuses on the asymptomatic stages of dementia, aims to find markers for early detection of cognitive impairment, and serves for both scientific types of research and preventive clinical trials in the field of normal aging and dementia (Chen et al., 2018; Yang et al., 2021). All enrolled participants were Han Chinese, 83 patients with AD and 38 NC were included in the current study. All participants received a standard dementia screening that included medical history, physical and neurological examinations, computed tomography (CT) or MRI of the brain, and neuropsychological testing. All enrolled participants (1) had no history of coronary disease, nephritis, tumors, neurological or psychiatric disorders, or addiction; (2) had no conditions known to affect cerebral function, including alcoholism, current depression, Parkinson's disease, or epilepsy; and (3) had no large vessel diseases, such as cortical infarcts or watershed infarcts, and subcortical infarcts. Dementia was diagnosed based on criteria modified from the DSM-5 (Regier et al., 2013) and further evaluated by brain CT or MRI. The diagnosis of AD was performed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). The NC denied any significant neuropsychiatric disease or memory trouble and had a mini-mental state examination (MMSE) score of 24 or higher.

Considering that the clinical manifestations of AD are related to the age of onset (Tellechea et al., 2018), we further divided the AD patients into early-onset AD ($n = 42$, age-onset <65 years) and late-onset AD ($n = 41$, age-onset ≥65 years) according to the age at onset. The differences in PET uptake patterns of tau, Aβ, and hypometabolism and their relationship with cognitive and behavioral symptoms between patients with early- and late-onset AD were explored in the supplementary analysis.

This study was approved by the Ethics Committee and Institutional Review Committee of Beijing Normal University and Beijing Tiantan Hospital, and all participants or their legal representatives gave their written informed consent.

2.2 | Neuropsychiatric assessment

In addition to the MMSE, all participants independently completed neuropsychiatric symptom assessment through the Neuropsychiatric Inventory (NPI) scale (Medeiros et al., 2010), which requires an interview between the informant and a clinician. The NPI scale has been accepted as a brief, reliable, informant-based assessment of NPS and has been widely used in NPS research (Trzepacz et al., 2013). It assesses 12 NPS from the informant's perspective: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, disinhibition, irritability, apathy, abnormal motor behavior, sleep disorders, and appetite disorders. In this study, these 12 NPS were used to classify each study participant as NPS positive or negative. Respondents identified changes in symptoms in the past 4 weeks by answering "yes" or "no". According to the respondent's judgment, the NPS of each participant was determined to be positive or negative.

2.3 | PET data acquisition

The participants underwent tau PET imaging with [^{18}F]flortaucipir (66 AD patients, 27 controls), Aβ PET imaging with [^{18}F]florbetapir (75 AD patients, 37 controls), and glucose metabolism PET imaging with [^{18}F] fluorodeoxyglucose (FDG) (54 AD patients, 27 controls) on a Discovery TM PET/CT Elite scanner (General Electric) at the Beijing Tiantan Hospital, Capital Medical University (Beijing, China). For tau PET, a 15-min emission PET scan was performed 80 min after injection of approximately 280 mCi of [^{18}F]flortaucipir. The 15-minute [^{18}F]florbetapir PET scan started 50 min after the intravenous injection of 10 mCi of the tracer. 10-min FDG-PET scans were acquired with study participants who fasted for at least 6 h before and 60 min after the injection of 185 ± 8 MBq of [^{18}F]FDG. Tau, Aβ, and hypometabolism PET scans were acquired on different days but within 1 week of each other.

2.4 | Data processing

Data processing was performed using Statistical Parametric Mapping 12 (SPM12, www.fil.ion.ucl.ac.uk/spm). First, flortaucipir and florbetapir images were realigned to their corresponding FDG images (Figure S1). Then, FDG, the realigned florbetapir, and the realigned flortaucipir images were spatially normalized into the MNI standard space using the normalization parameters obtained from the FDG normalization. All images were spatially smoothed with a 10-mm Gaussian kernel. Standardized uptake value ratios (SUVR) were calculated using cerebellar gray matter as a reference region for all three PET modalities.

In addition, we calculated the mean image of the spatially normalized and reference-count–scaled flortaucipir and florbetapir images to generate the flortaucipir and florbetapir templates, respectively, used for 40 patients without FDG images. For the 40 participants without FDG images, their flortaucipir and florbetapir image normalizations into MNI standard space were performed using the corresponding customized template for tau or Aβ separately. The other processing steps were the same.

2.5 | Statistical analyses

To examine group differences in age, education, and cognitive performance, two-sample *t*-tests were performed while the χ^2 test was applied for sex.

(1) To explore the similarities and differences among tau, Aβ, and hypometabolism spatial distributions in the patients with AD, we performed voxel-based two-sample *t*-tests in each of the three PET techniques comparing AD and controls after controlling for age, sex, and education. We used the false discovery rate (FDR, $q < 0.05$) to correct for multiple comparisons. We further identified brain regions where tau overlaps with Aβ and FDG respectively that showed specific damage of tau, common damage of tau and Aβ, or common damage of tau and hypometabolism in AD patients. In the supplementary analysis, we also investigated the overlap regions of Aβ and FDG and quantitatively calculated the corresponding voxel percentage. Specifically, we used $q < 0.05$ to define the spatial pattern for each PET technique and then conducted a set intersection operation to identify the tracer-specific damage for a given tracer (Tau-only damage, Aβ-only damage, or FDG-only damage), the overlap between any two of them (Tau & Aβ, Tau & FDG, Aβ & FDG) or overlap for all three tracers (Tau & Aβ & FDG). Then, we calculated the percentage of each region's volume to the total damaged region's volume for tau, Aβ, and FDG in the AD patients. Finally, we calculated the mean SUVR of these regions for subsequent analyses, including their use for differential or combined power for clinical diagnosis.

Piecewise linear regression analysis against MMSE scores (i.e., MMSE as the independent variable) was used to delineate the trajectory of tau, Aβ, and hypometabolism along with cognitive impairment severity and to identify key inflection points. For tau, we performed the regression of the tau mean SUVR of four regions (tau-only region, tau and Aβ overlapping region, tau and FDG overlapping region, tau, Aβ, and FDG overlapping region) against the MMSE scores. Similarly, the same analytic procedure was separately applied to Aβ-PET and FDG-PET data. For the piecewise regression, we first used locally weighted (LOESS) regression to determine the number of inflection points and range, which provided the initial value of the nonlinear regression model, and then, based on the piecewise linear model of the Gauss-Newton iteration, obtained the final piecewise linear curve fit (Li et al., 2014).

Then, we used pairwise correlation analyses to explore tau-Aβ, tau-hypometabolism, and Aβ-hypometabolism inter-relationships in AD patients based on the four specific-damaged and co-damaged regions indicated by tau, Aβ, and hypometabolism biomarkers.

(2) To identify whether the NPS in AD patients was associated with cognitive decline, we performed a logistic regression analysis with each item of the NPI scale as the dependent variable and MMSE scores as a predictor controlling for age, sex, and education. Furthermore, for each of the 12 NPI items, the AD patients were divided into two groups, with or without NPS. To evaluate the differences in tau, Aβ, and hypometabolism between the two groups, we performed two-sample *t*-tests.

(3) To compare the performance of tau, Aβ, and hypometabolism for the diagnosis of AD, we used support vector machine to classify AD and NC groups based on the above mentioned identified four regions of tracer-specific and co-damage for each molecular imaging marker together. To evaluate the performance of our classification methods, we used a leave-one-out strategy and receiver operating characteristic curves to compute the classification accuracy, as well as the sensitivity and specificity.

(4) To investigate the effect of age at onset of AD on the association between molecular imaging biomarkers with cognitive and behavioral symptoms, we used the voxel-based two-sample *t*-tests to identify lesion regions of tau, Aβ, and hypometabolism in early- and late-onset AD compared with controls after controlling for age, sex, and education, and calculated the mean SUVR of these regions. As described above, piecewise linear regressions were performed against MMSE scores to delineate the trajectory of the mean SUVR of tau, Aβ, and hypometabolism along with cognitive impairment, and two-sample *t*-tests were performed to evaluate the differences in tau, Aβ, and hypometabolism between groups with or without NPS in early- and late-onset AD patients.

3 | RESULTS

3.1 | Clinical characteristics of participants

The participant characteristics are shown in Table 1. Age ($p = .74$) and years of education ($p = .124$) did not differ between the 83 patients and 38 controls, and there were more females in the AD patient than in the control group ($p = .051$). Compared with the controls, the AD patients had a more impaired overall cognitive ability (MMSE; $p < .001$).

3.2 | The regions with tau accumulation overlapped extensively with the hypometabolism regions, and the deposition regions of Aβ were unique

First, we performed voxel-wise ANCOVA separately for [^{18}F]flortaucipir, [^{18}F]florbetapir, and [^{18}F]FDG PET between patients and controls. Furthermore, we separately identified the brain regions where the AD patients had higher flortaucipir and florbetapir and lower FDG SUVR than the NC (Figure 1a; Table S1). In contrast, tau accumulation is region-specific and mainly occurred in inferior temporal lobes in AD patients. For Aβ in patients, greater deposition of Aβ was mainly observed in the superior and middle frontal, inferior and middle temporal, and putamen regions. Significant hypometabolism in the patients was found in the medial and posterior cingulate gyrus, precentral gyrus, superior and middle frontal gyrus, and occipital lobe. For AD patients with all three PET imaging, their uptake patterns of Flortaucipir, Florbetapir, and FDG were consistent with the above results (Figure S2).

It is not surprising that the spatial distribution patterns of tau, Aβ, and hypometabolism were not completely overlapped. By using the intersection operation in set theory, we defined the tracer-specific and common-damage for each molecular imaging marker pair, and both were expressed as the percentage of the total damaged region volume of the given tracer-specific pattern (Figure S3). For tau, most of the tau-damaged areas overlapped with the hypometabolism-damaged areas, accounting for 52.94% of the total tau-damaged areas; and 20.33% of the total tau-damaged areas overlapped with the Aβ-damaged areas (Figure 1b,c). While for Aβ, most of the damaged brain areas were unique to Aβ, accounting for 60.98% of the total area of Aβ damage in the patients. For hypometabolism, the areas of the brain affected by hypometabolism were widely distributed. The common-damaged areas of tau, Aβ, and hypometabolism were mainly in the left inferior temporal lobe (Figure S3).

3.3 | Tau accumulation is closely related to hypometabolim, not to Aβ

Next, we used pairwise correlation analyses to explore the within-modality region pairwise associations and between-modality tracer pairwise associations in the AD patients. The results showed that the accumulation of tau in different regions was also closely correlated. Simultaneously, the accumulation of tau in both Tau & Aβ common-damaged areas and Tau & Aβ & FDG common-damaged areas was

TABLE 1 Demographics and neuropsychological test scores of patients with Alzheimer's disease and normal controls

	AD ($n = 83$)	NC ($n = 38$)	t or X^2	p
Age (years)	64.93 ± 9.181	64.32 ± 9.870	0.332	.740
Sex (M/F)	41/42	26/12	3.817	.051
Education (years)	9.57 ± 4.563	10.99 ± 4.839	−1.551	.124
MMSE	12.46 ± 6.550	26.95 ± 1.659	−18.674	**<.001**

Abbreviations: AD, Alzheimer's disease; F, female; M, male; MMSE, mini-mental state examination; NC, normal controls.

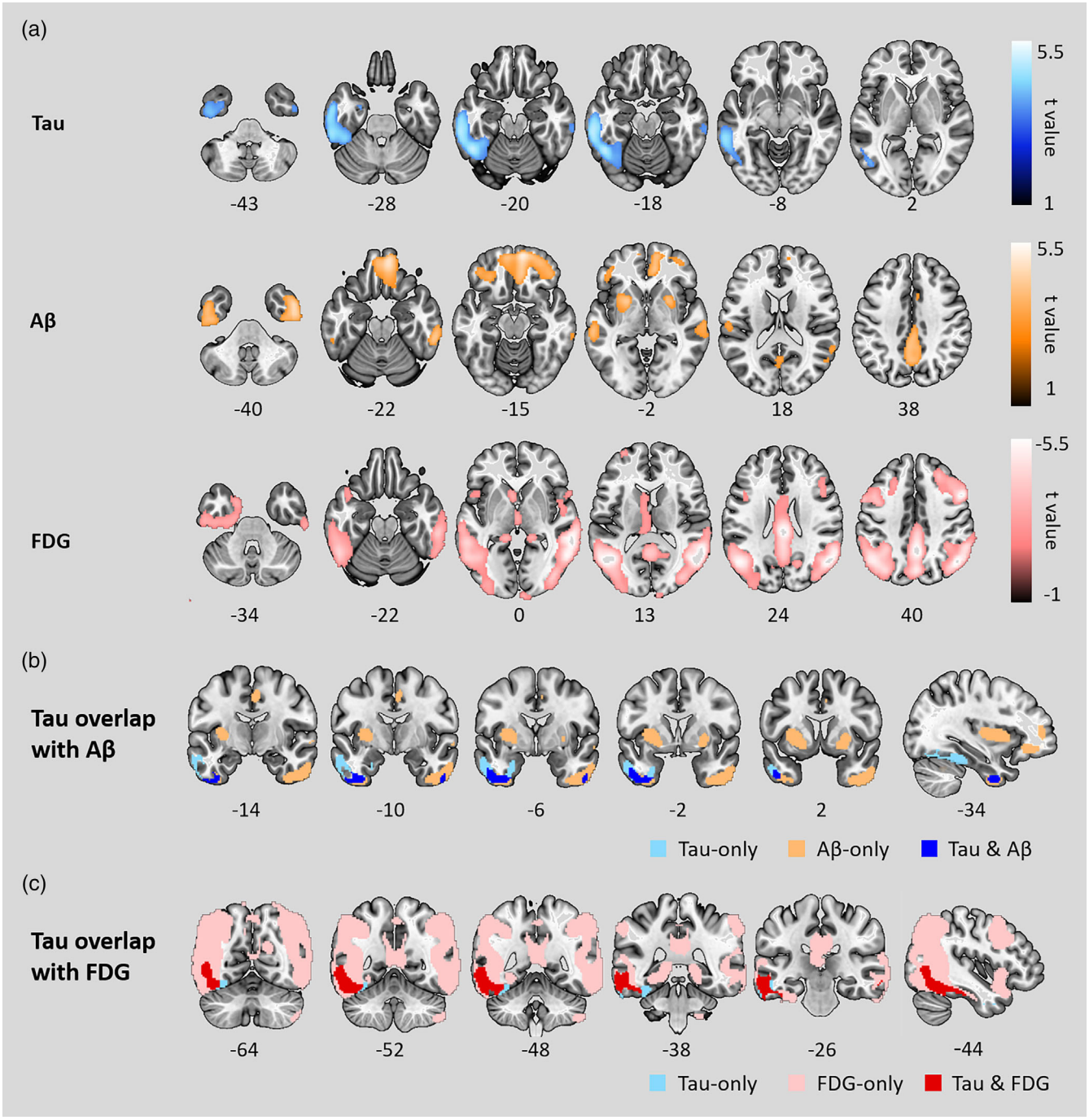

FIGURE 1 Tau accumulation overlapped extensively with the hypometabolism regions, and the deposition regions of Aβ were unique. (a) The top row shows the regions of significant deposition of tau in the AD patients compared to the normal controls. The middle row represents the regions of significant accumulation of Aβ. The bottom row shows the regions of significant hypometabolism. The color bar represents the t value of voxel-wise two-sample *t*-tests, and the brighter color represents the higher t value. All these results were corrected by FDR ($q = 0.05$). (b) The tau-damaged areas overlapped with the Aβ-damaged areas. (c) The tau-damaged areas overlapped with the hypometabolism-damaged areas. AD, Alzheimer's disease; Aβ, amyloid-β

closely related to multiple areas of hypometabolism (Table 2, $p < .05$). Similarly, hypometabolism across different regions was closely related (Table 2, $p < .01$). For Aβ, the deposition of Aβ in different brain regions was strongly correlated with each other (Table 2, $p < .01$), while there were no correlations of Aβ with tau or hypometabolism in the same or different damaged areas.

3.4 | Unlike Aβ, tau and hypometabolism build up monotonically with increasing cognitive impairment in the late stages of AD

The results of the piecewise linear regression showed that the accumulation of tau in the AD patients started relatively slowly, at

TABLE 2 Tau accumulation is closely related to hypometabolism, not to Aβ

	Region mean SUVR of tau				Region mean SUVR of Aβ				Region mean SUVR of hypometabolism			
	Tau-only	Tau & Aβ	Tau & FDG	Tau & Aβ & FDG	Aβ-only	Aβ & tau	Aβ & FDG	Aβ & tau & FDG	FDG-only	FDG & Aβ	FDG & tau	FDG & tau & Aβ
Region mean SUVR of Tau												
Tau-only	1.00	0.83[b]	0.92[b]	0.88[b]	0.26	0.21	0.30	0.26	−0.04	−0.21	−0.28	−0.33
Tau & Aβ		1.00	0.80[b]	0.92[b]	0.24	0.13	0.26	0.22	−0.32	−0.47[b]	−0.47[b]	−0.46[b]
Tau & FDG			1.00	0.89[b]	0.28	0.19	0.31	0.29	−0.03	−0.14	−0.26	−0.30
Tau & Aβ & FDG				1.00	0.27	0.20	0.31	0.31	−0.28	−0.36[a]	−0.42[a]	−0.37[a]
Region mean SUVR of Aβ												
Aβ-only					1.00	0.82[b]	0.96[b]	0.85[b]	−0.06	−0.06	−0.15	0.06
Aβ & Tau						1.00	0.82[b]	0.92[b]	−0.07	−0.07	−0.14	0.04
Aβ & FDG							1.00	0.88[b]	−0.08	−0.08	−0.21	0.03
Aβ & Tau & FDG								1.00	−0.16	−0.15	−0.24	−0.01
Region mean SUVR of FDG												
FDG-only									1.00	0.89[b]	0.77[b]	0.52[b]
FDG & Aβ										1.00	0.80[b]	0.63[b]
FDG & Tau											1.00	0.84[b]
FDG & Tau & Aβ												1.00

Note: The values in the table are the *r* values of Pearson's correlation. [a]$p < .05$; [b]$p < .01$.
Abbreviations: Aβ, amyloid-β; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratios.

an MMSE score of ~22 points, and the accumulation speed of most tau begins to increase with the decline in cognitive function after the inflection point (Figure 2a; Table S2; the approximate 95% confidence interval of the estimated rate of slope change respectively after the inflection point was −0.025 to −0.003 for the tau mean SUVR in the tau-only damaged region, −0.027 to −0.0001 for the tau mean SUVR in the Tau & Aβ co-damaged region, −0.031 to −0.003 for the tau mean SUVR in the Tau & FDG co-damaged region and − 0.031 to −0.003 for the tau mean SUVR in the Tau & Aβ & FDG co-damaged region). Nevertheless, there was no significant correlation between increased deposition of Aβ and cognitive decline as measured with MMSE in the patients with AD (Figure 2b; Table S2), which may be due to Aβ deposition starting earlier, almost reaching a plateau once AD dementia had developed.

Compared with tau, the critical period of hypometabolism was at the late stage, appearing at an MMSE score between 10 and 19 points, and the decreases in metabolism after the inflection point were significantly correlated with MMSE scores (Figure 2c; Table S2; the approximate 95% confidence interval of the estimated rate of slope change respectively after the inflection point was 0.002 to 0.014 for the metabolism mean SUVR in the FDG-only damaged region, 0.004 to 0.051 for the metabolism mean SUVR in the FDG & Aβ co-damaged region, 0.003 to 0.024 for the metabolism mean SUVR in the FDG & Tau co-damaged region, and 0.001 to 0.02 for the hypometabolism mean SUVR in the FDG & Tau & Aβ co-damaged region).

3.5 | Hypometabolism and tau had higher accuracy in differentiating the AD patients from controls than Aβ

AD-related brain regions had an excellent discrimination accuracy for AD patients and normal controls (Figure 3a; Table S3). For the three molecular imaging biomarkers, tau yielded the highest specificity of 0.96 (accuracy = 0.85, AUC = 0.86, sensitivity = 0.64). Aβ yielded the highest sensitivity of 0.87 (accuracy = 0.81, AUC = 0.84, and specificity = 0.73). Hypometabolism yielded the highest classification accuracy of 0.88 (AUC = 0.88, sensitivity = 0.78, and specificity = 0.89). Therefore, hypometabolism and tau had higher accuracy in differentiating the AD patients from controls than Aβ.

Next, we used multimodal PET data to discriminate AD patients from controls and found that the accuracy increased (Figure 3b; Table S3). When the three molecular imaging markers were used together, the classification achieved the highest accuracy of 0.95, the highest AUC of 0.95, and the highest sensitivity of 0.97.

3.6 | NPS in AD were associated with tau deposition closely, followed by hypometabolism, but not with Aβ

The logistic regression model with NPS as the dependent variable and MMSE score as the independent variable showed that there was a significant relationship between NPS and cognitive impairment (Table 3).

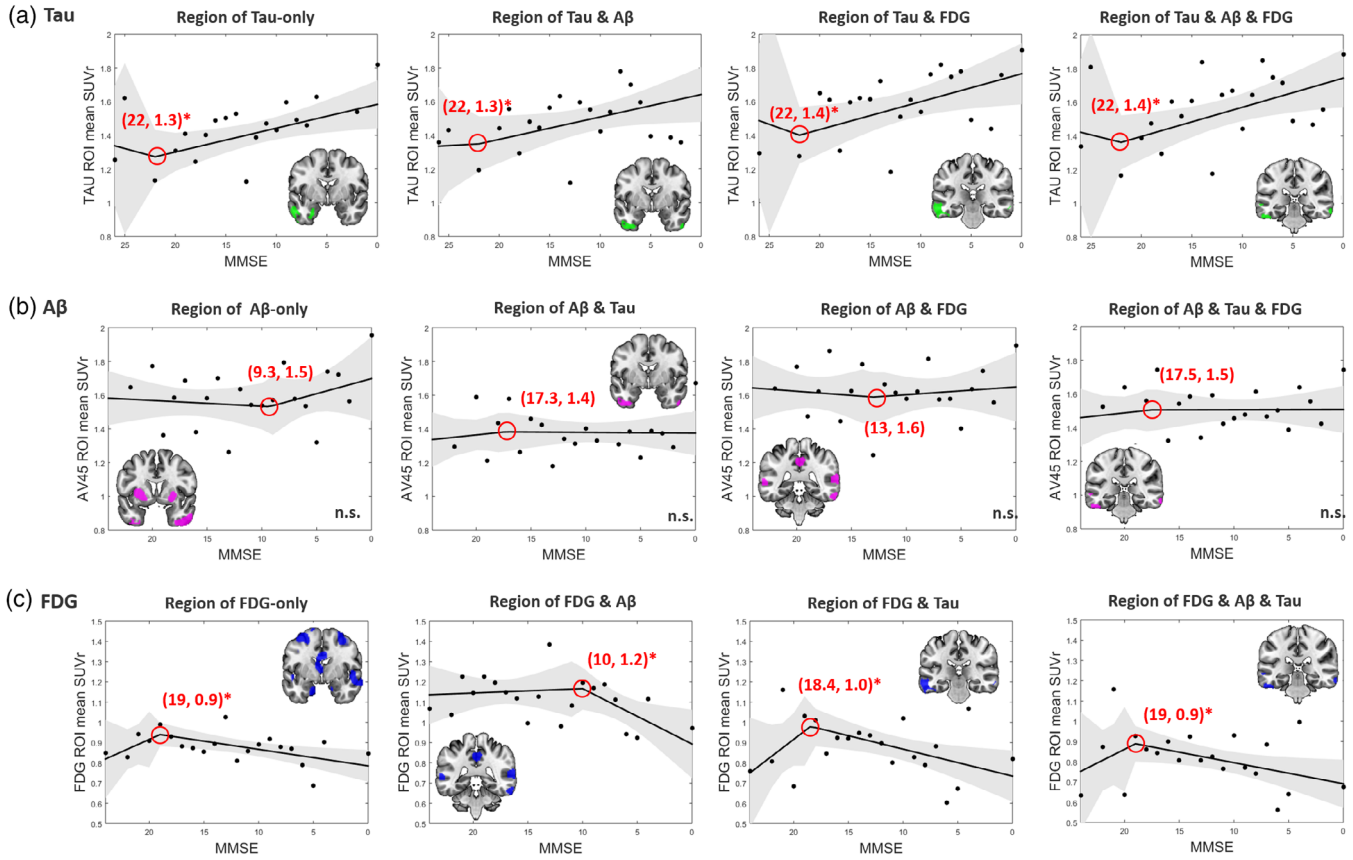

FIGURE 2 Trajectories of cognitive-related molecular imaging biomarkers in AD patients fitted using piecewise linear regression analysis. The black dots represent the averages of mean PET SUVR at each MMSE score. Solid lines represent local linear variations with MMSE in tau, Aβ, or FDG. Shaded areas represent 95% confidence intervals. Pentagonal stars (*) represent the piecewise linear regression with a significant value. (a) The vertical coordinates of the four figures are the mean tau SUVR value of the tau-only damaged region, common damaged region of tau and Aβ, common damaged region of tau and FDG, common damaged region of tau, Aβ, and FDG, and the horizontal coordinate is the MMSE score. (b) The vertical coordinates of the four figures are the mean Aβ SUVR value of Aβ-only damaged region, common damaged region of Aβ and tau, common damaged region of Aβ and FDG, common damaged region of Aβ, tau, and FDG, and the horizontal coordinate is the MMSE score. (c) The vertical coordinates of the four figures are the glucose metabolism mean SUVR value of FDG-only damaged region, common damaged region of FDG and Aβ, common damaged region of FDG and tau, common damaged region of FDG, tau, and Aβ, and the horizontal coordinate is the MMSE score. AD, Alzheimer's disease; MMSE, mini-mental state examination; Aβ, amyloid-β; FDG, fluorodeoxyglucose; MMSE, mini-mental state examination; PET, positron emission tomography; SUVR, standardized uptake value ratios

Cognitive performance was a significant predictor in the AD patients for delusion ($p = .018$), hallucination ($p < .001$), agitation ($p = .005$), apathy ($p = .014$), disinhibition ($p = .014$), and aberrant motor behavior ($p < .001$).

Compared with Aβ and hypometabolism, NPS was more related to tau (Table 4; Figure 4). Higher tau deposition was observed in the AD patients who had depression (Tau-only areas: $p < .001$; Tau & Aβ areas: $p = .003$; Tau & FDG areas: $p = .001$; Tau & Aβ & FDG areas: $p < .001$), apathy (Tau-only areas: $p = .046$; Tau & FDG areas: $p = .011$), aberrant motor behavior (Tau-only areas: $p = .032$), or eating disorder (Tau-only areas: $p = .032$; Tau & Aβ areas: $p = .046$; Tau & FDG areas: $p = .043$; Tau & Aβ & FDG areas: $p = .026$). Anxiety in the AD patients was associated with hypometabolism (FDG-only areas: $p = .039$). However, we did not find strong evidence of a neuropsychiatric relationship with Aβ.

Our data suggest that the most prominent NPS in the AD were apathy, irritation, and agitation, which accounted for more than 50% of the clinical AD patients (Figure S4). The second most prominent NPS were eating disorder, aberrant motor behavior, anxiety, and sleep disorder, all in the proportion of 30%–50% of the patients. Other NPS all were more than 10% as well.

3.7 | Effects of age at onset of AD on the relationship between tau, Aβ, and hypometabolism with cognitive and behavioral symptoms

Finally, we wondered whether the pathological spatial patterns of tau, Aβ, and hypometabolism and their relationship with cognitive and behavioral symptoms were the same in the early- and late-onset AD. The demographics of 42 early-onset AD and 41 late-onset AD are shown in Table S4.

Voxel-based morphometry analysis showed that although tau accumulation was more extensive in early-onset AD than in late-onset

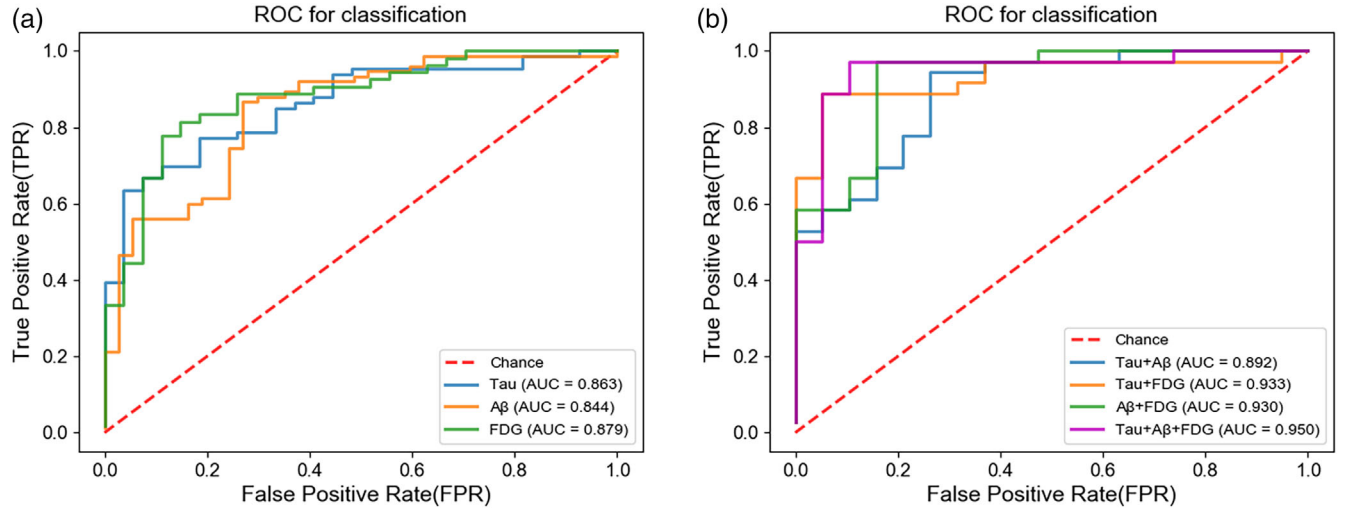

FIGURE 3 Hypometabolism and tau had higher accuracy in differentiating the AD patients from controls than Aβ, but the combined three had the highest accuracy. (a) ROC curve for the classification sensitivity and specificity obtained by using single molecular imaging markers. (b) ROC curve for the classification sensitivity and specificity obtained by using the multimodal combination of molecular imaging biomarkers. AD, Alzheimer's disease; Aβ, amyloid-β; ROC, receiver operating characteristic curves

TABLE 3 The relationship between cognitive performance as measured with MMSE and neuropsychiatric symptoms in patients with Alzheimer's disease

	MMSE	
	Odds ratio (95% CI)	***p*-Value**
Delusion	0.891 (0.809–0.980)	**.018**
Hallucination	0.751 (0.640–0.882)	**<.001**
Agitation	0.883 (0.809–0.963)	**.005**
Depression	0.945 (0.878–1.017)	.132
Anxiety	0.989 (0.920–1.064)	.772
Euphoria	0.917 (0.811–1.036)	.165
Apathy	0.889 (0.809–0.976)	**.014**
Disinhibition	0.877 (0.790–0.973)	**.014**
Irritation	0.932 (0.864–1.006)	.070
Aberrant motor behavior	0.843 (0.767–0.928)	**<.001**
Sleep disorder	0.999 (0.927–1.077)	.988
Eating disorder	0.963 (0.895–1.037)	.320

Note: The odds ratio of the logistic regression for the cognitive score is described, along with their statistical significance (*p*-value). Statistically significant effects ($p < .05$) are in bold.
Abbreviation: MMSE, mini-mental state examination.

AD, tau pathology was region-specific in both cases, mainly occurring in the inferior temporal lobe (Figure S5, Tables S5 and S6, $p < .0005$). For Aβ in early-onset AD, greater deposition of Aβ was mainly observed in the inferior and middle temporal, middle and inferior frontal, and anterior cingulate regions, while the deposition of Aβ was observed only in the medial frontal, precuneus, and putamen regions in late-onset AD ($p < .0005$). Both early- and late-onset AD patients had significant hypometabolism in the neocortex, but the former had more extensive damage, including the middle, inferior, and superior temporal, inferior parietal, and middle occipital regions ($p < .0005$).

The results of piecewise linear regression showed that the accumulation of tau was linearly correlated with MMSE scores in both early-onset AD (Figure S6, 95% CI of the slope: −0.025 to −0.003) and late-onset AD (95% CI of the slope: −0.035 to −0.001) in the whole process of cognitive decline. In other words, the accumulation of tau associated with cognitive level has increased in the early stages of cognitive impairment (MMSE > 26). In contrast, the critical period of hypometabolism was in the later stage of cognitive impairment, and hypometabolism was significantly positively associated with decreased MMSE scores after the 19-point in early-onset AD (95% CI of the slope: 0.005–0.024) and 10-point late-onset AD (95% CI of the slope: 0.006–0.040). Nevertheless, there was no significant correlation between increased deposition of Aβ and cognitive decline as measured with MMSE in early- and late-onset AD.

Similarly, tau and glucose metabolism levels, but not Aβ, were associated with NPS in early- or late-onset AD (Table S7, Figure S7). Specifically, tau deposition was increased in early-onset AD patients with depression ($p < .001$), and late-onset AD patients with depression ($p = .032$) or apathy ($p = .014$). Glucose metabolism was decreased in late-onset AD patients with delusion ($p = .042$) or hallucination ($p = .005$). There was no correlation between Aβ deposition and NPS ($p > .05$).

4 | DISCUSSION

In the current study, the spatial patterns of tau, Aβ, and hypometabolism in AD patients were first investigated and determined. We found that the accumulation of tau was closely related to the hypometabolism, and the deposition of Aβ was not correlated with tau and

TABLE 4 Neuropsychiatric symptoms in Alzheimer's disease were associated with tau deposition closely, followed by hypometabolism, but not with Aβ

	Region mean SUVR of tau				Region mean SUVR of Aβ				Region mean SUVR of FDG			
	Tau-only	Tau & Aβ	Tau & FDG	Tau & Aβ & FDG	Aβ-only	Aβ & tau	Aβ & FDG	Aβ & tau & FDG	FDG-only	FDG & Aβ	FDG & tau	FDG & tau & Aβ
Delusion												
Hallucination												
Agitation												
Depression	√	√	√	√								
Anxiety									√			
Euphoria												
Apathy	√		√									
Disinhibition												
Irritation												
AMB	√											
Sleep												
Eating	√	√	√	√								

Note: Statistically significant effects are indicated by tick marks ($p < .05$).
Abbreviations: Aβ, amyloid-β; AMB, aberrant motor behavior; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratios.

hypometabolism in AD patients. Second, we demonstrated that when patients had developed AD, Aβ did not continue to build-up monotonically with cognitive decline measured with MMSE. In contrast, tau and hypometabolism were closely related to cognitive changes, and the key inflection points were MMSE scores of 22 points and 10–19 points, respectively. Next, the results showed that hypometabolism and tau have higher accuracy in differentiating AD patients from controls than Aβ. When the three molecular imaging biomarkers were used together, the discriminating accuracy was improved accordingly. Finally, we determined that the NPS in the AD patients was associated with cognitive decline measured with MMSE and tau deposition closely, followed by hypometabolism, but not with Aβ. In addition, the association between cognitive and behavioral symptoms and molecular imaging markers in AD was independent of age at onset.

Several previous studies have found that biomarkers of tau, Aβ, and hypometabolism are associated with clinical features of AD (Gordon et al., 2019; Jagust, 2018; Mattsson et al., 2019; Takahata et al., 2019). However, studies directly comparing these processes and their effects on diagnosis, cognition, and NPS in AD are rare. Our findings suggest that although Aβ plaques may play a key role in the early stage of AD, tau pathology and glucose metabolism are superior over Aβ to identify AD and cognitive impairment, and tau accumulation is associated with NPS closely.

4.1 | Tau accumulation is the key influencing factor of NPS in patients with AD

The present study supported that NPS is one of the main clinical symptoms and could influence the factors of AD. Our results showed that the majority of NPS were associated with cognitive impairment measured with MMSE in AD patients, which is consistent with previous research findings (Craig et al., 2005; Zhao et al., 2016). For example, the prevalence of hallucination, aberrant motor behavior, delusion, and sleep disturbance were significantly higher in moderate or severe AD than in mild AD (Chen et al., 2021; Cheng et al., 2012). In addition, our results showed that AD-related tau accumulation was significantly correlated with NPS, including depression, apathy, aberrant motor behavior, and eating disorders. This fits into the evolving framework that tau appears to be closely associated with cognitive symptoms of AD (Ossenkoppele et al., 2016), rather than Aβ.

As one of the most widely used tau PET tracers, [^{18}F]flortaucipir PET has been proved to be a reliable biomarker of advanced Braak tau pathology in AD by PET-to-autopsy studies (Fleisher et al., 2020; Soleimani-Meigooni et al., 2020). This tracer was appropriate for our study sample, where most AD patients were at an advanced stage of the disease (the mean MMSE score was 12.5). But this tracer may not detect early Braak stages of neurofibrillary tangle pathology (Soleimani-Meigooni et al., 2020). Further research is needed to determine whether earlier stages of tau pathology can be detected with PET and the relationship between tau PET and NPS in the early stages of AD.

Meanwhile, a correlation between AD-related hypometabolism and anxiety was found in the current study, while we did not find a correlation between AD-related Aβ deposition and NPS. However, previous studies showed anxiety was related to the high burden of Aβ in the frontal lobe in the mild cognitive impairment (Bensamoun et al., 2015), and the combination of anxiety and high Aβ burden led to a more rapid cognitive decline in preclinical AD (Pietrzak et al., 2015). Therefore, in combination with previous research findings and current research results, Aβ may be associated with NPS in the early stage of the disease, while tau accumulation is the key influencing factor of NPS in patients with AD.

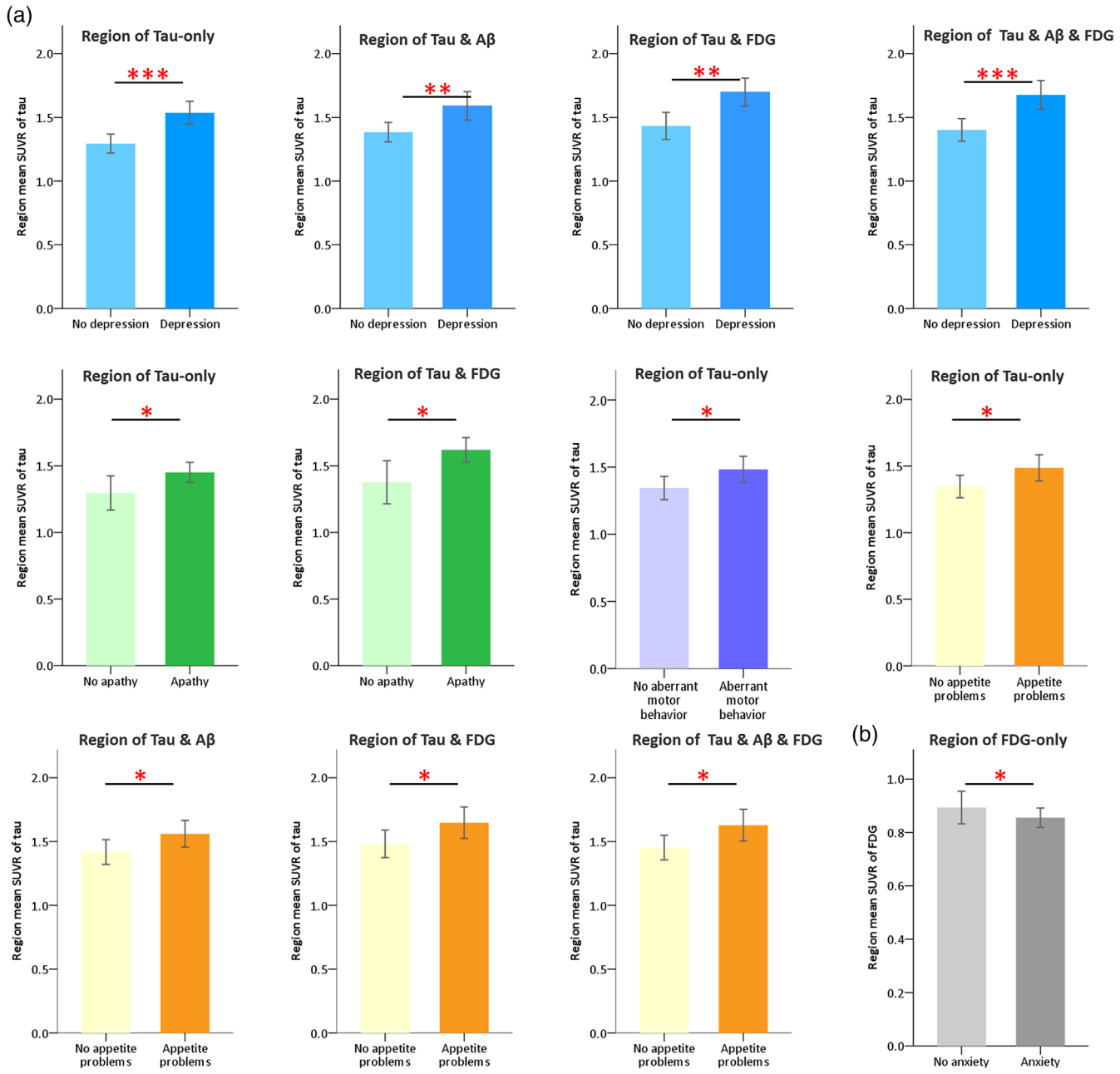

FIGURE 4 Neuropsychiatric symptoms in AD were associated with tau deposition closely, followed by hypometabolism. (a) The bar graph shows that the mean ROI SUVR of tau PET of the AD patients with NPS (depression: Blue; apathy: Green; aberrant motor behavior: Purple; appetite disturbance: Yellow) is significantly higher than that of the patients without NPS. (b) The bar graph shows that the mean ROI SUVR of FDG PET of the AD patients with anxiety symptoms is significantly lower than that of the patients without anxiety symptoms. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. AD, Alzheimer's disease; Aβ, amyloid-β; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUVR, standardized uptake value ratios; ROI, region of interest

4.2 | Tau deposition regions overlapped more extensively with the hypometabolism regions

The aggregation of Aβ and tau is thought to play a crucial role in a neurodegenerative cascade that results in the loss of neurons and synapses (Duyckaerts et al., 2009). Consistent with previous studies (Ossenkoppele et al., 2016), we found that tau pathology was strongly co-located with hypometabolism regions, and the level of tau deposition was closely related to hypometabolism (Table 2). In contrast, most AD-related Aβ distribution regions were independent and different from tau and hypometabolism. These findings support the disease model that neurodegeneration of AD is mainly caused by tau neurofibrillary tangles and both share vulnerabilities or synergistic toxic mechanisms (La Joie et al., 2020). Interestingly, Aβ, tau, and hypometabolism only overlapped in the left inferior temporal lobe region, so this area may be the most specific region for the AD

biomarkers of disease progression. A better understanding of these relationships could provide greater insight into disease pathogenesis and inform the integration of multimodal neuroimaging into therapeutic trials and drug development.

4.3 | Tau and hypometabolism may be more correlated with cognitive decline than Aβ

Previous reviews revealed that there is insufficient evidence to suggest that Aβ is related to cognition in AD patients; on the contrary, tau and hypometabolism may be more correlated with cognitive decline (Hammond & Lin, 2022; Lagarde et al., 2022; Morris et al., 2018; Ossenkoppele et al., 2021), which is consistent with the results of the current study. The reason may be that these lesions occur in different anatomical locations and spatially spread across regions. The diffusion location for tau starts in the lower cortex and moves from the transentorhinal region to the neocortex (Adams et al., 2018; Kim et al., 2018) which may have a stronger spatial correlation with the degeneration region (Ossenkoppele et al., 2016). However, Aβ spreads in the opposite direction (Goedert, 2015; Thal et al., 2002). Another reason may be that Aβ in the brain occurs approximately 15–30 years before the onset of AD clinical symptoms (Sperling et al., 2011), and the accumulation of Aβ has almost reached a plateau when patients had progressed into AD, so it is necessary to explore the relationship between Aβ and cognition at an earlier stage of AD in subsequent studies.

More importantly, we found that the critical period of hypometabolism was in the later stage of cognitive impairment compared with tau. A recent study came to similar conclusions, finding that tau drives early AD decline while glucose hypometabolism drives late decline (Hammond et al., 2020). Another study further showed that local glucose metabolism had a mediating effect on the relationship between tau retention in temporal regions and global cognition (Saint-Aubert et al., 2016). These findings confirmed the theoretical model of AD pathophysiology that tau pathology precedes neuronal dysfunction (as identified by [18F]FDG PET) and that further affects the downstream cognitive process (Jack Jr et al., 2010). In the treatment of AD, glucose metabolism may be more appropriate as a target for advanced AD, rather than early or overall AD pathology.

4.4 | Hypometabolism and tau had higher accuracy in differentiating the AD patients from controls than Aβ

Due to the widespread accumulation of Aβ in normal elderly people (Ossenkoppele et al., 2018), Aβ lacks specificity as a biomarker for the clinical diagnosis of AD (Jansen et al., 2015). In the current study, the specificity was only reached to 0.73 when Aβ was used to classify AD patients and NC, while the specificity of tau and hypometabolism was reached to 0.96 and 0.89, respectively. In contrast, Aβ was more sensitive to the diagnosis of AD. Meanwhile, the accuracy of diagnosis of AD using multiple molecular imaging biomarkers in this study was higher than that of any single imaging biomarker, which confirmed that tau and hypometabolism served as additional indicators that can improve diagnostic performance.

4.5 | Cognitive and behavioral symptoms in early- or late-onset AD were associated with tau and hypometabolism

The results of the supplementary analysis showed that early-onset AD has a greater pathologic burden of tau, Aβ, and glucose metabolism relative to late-onset AD, which is consistent with previous most postmortem (Bigio et al., 2002; Marshall et al., 2007) and PET research findings (Cho et al., 2013; Kim et al., 2005; Schöll et al., 2017). More importantly, although cognitive or behavioral symptoms of AD are associated with tau or hypometabolism pathology, it is currently unknown whether this association is affected by age at onset. A recent study found a correlation between tau pathology burden and MMSE score in both early- and late-onset AD (Visser et al., 2022), which is consistent with our findings. In addition, our result showed that cognitive level is also associated with hypometabolism in the later stages of cognitive impairment. For behavioral and psychiatric symptoms, we found that tau was associated with affective symptoms, especially depression, in both early- and late-onset AD, and hypometabolism was marginally associated with psychosis symptoms only in late-onset AD. These findings contribute to the understanding of differences between early-onset and late-onset AD, and more data are needed to validate these findings in the future.

4.6 | Limitations

This study has several limitations. First, we focused only on whether NPS was associated with tau, Aβ, hypometabolism or cognition, so NPS was treated as a categorizing variable instead of a continuous variable. In future studies, it is necessary to further investigate the NPS score as a continuous variable and explore the association between NPS severity and neuroimaging changes in a larger AD sample. In addition, the PET data were not partial volume corrected. Although some previous PET studies had not been partial volume corrected (Jack Jr et al., 2017; Knopman et al., 2019), and some had shown little change after partial volume correction, there remains the possibility that the results may not be accurate enough.

5 | CONCLUSIONS

In conclusion, our analysis provided additional information on the spatial distributions of tau, Aβ, and glucose metabolism in AD patients. Overall, our study demonstrated that the Aβ load in the brain reaches a plateau during the progression of AD and tau correlates better to cognitive and neuropsychiatric symptoms and together with cerebral

hypometabolism discriminates AD from controls. These findings supported that tau pathology is a biomarker that still changes after progression to AD and may be more sensitive to the changes in emotional, mental, and behavioral symptoms of AD.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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