Correlation between Brain 18F-AV45 and 18F-FDG PET Distribution Characteristics and Cognitive Function in Patients with Mild and Moderate AD

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Research

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Abstract

Background

The purpose of this study is to investigate the characteristics of amyloid beta (Aβ) load and fluorodeoxyglucose (FDG) metabolism and analyze their correlation with cognitive impairment in the cerebral cortex of Alzheimer's disease (AD) patients using ^{18}F-florbetapir (^{18}F-AV45) and ^{18}F-FDG PET technology.

Methods

27 patients with AD were enrolled. All AD patients underwent detailed clinical and imaging examinations of the nervous system, completed the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests, and finished 18F-AV45 and 18F-FDG PET scans. NeuroQ software was used to analyze PET images.

Results

81.48% (22 out of 27) AD patients had significantly increased Aβ load and 96.30% (26 out of 27) had significantly reduced FDG metabolism. Moderate AD patients had more brain areas of reduced FDG metabolism with more severe reduction in some brain regions compared with mild AD patients, despite there was no differences of Aβ load between these patients. The range of reduced FDG metabolism was negatively correlated with the total scores of MMSE and MoCA, and the degree of FDG metabolism in some brain regions was positively correlated with the total score of MMSE and MoCA.

Conclusion

Brain ^{18}F-AV45 and ^{18}F-FDG imaging may be potential biomarkers of AD, and ^{18}F-FDG imaging is correlated with the degree of cognitive impairment in AD patients.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly. By 2050, it is expected that 115 million people will suffer from AD worldwide, which will cause great distress and economic burden to the patients, caregivers and society [1]. The clinical characteristics of AD are the progressive decline of cognitive ability, the continuous deterioration of episodic memory and the decline of living ability [2]. The disease has an unique neuropathology, including extracellular neurotrophic β-amyloid (Aβ) plaque deposition and intracellular neurofibrillary tangles (NFT) [3]. The abnormal accumulation of Aβ in the central nervous system is one of the important signs of AD. It can cause

synaptic dysfunction, synapse loss, and neuronal death in the brain, and then decline in cognitive ability [4]. Many studies have found that Aβ has neurotoxicity, and its toxicity depends on its primary structure and aggregation state [5]. Humans have two forms of Aβ, consisting of 40 or 42 amino acid residues, namely Aβ1–40 and Aβ1–42. Aβ1–42 is extremely important for the development of AD, which is more prone to aggregation and has higher toxicity than Aβ40 [6]. Aβ molecules can form low molecular weight oligomers and high molecular weight oligomers (such as fibrils). Fibrils can directly cause neuronal dysfunction by acting on synapses or activate astrocytes and microglia to indirectly damage neuron [5, 6].

In 2011 revision of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria of AD diagnosis, imaging biomarkers including neurodegeneration markers and amyloid deposition markers have been incorporated [7]. These changes can be investigated in detail by positron emission tomography (PET). ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET can detect the level of glucose metabolism in specific areas in the brain to reflect the function and the number of neurons [8]. ^{18}F-florbetapir (^{18}F-AV45) PET is used to mark the amyloid load [9].^{18}F-AV45 has a high affinity with Aβ and does not bind to tau or synuclein at the binding site of Aβ with high sensitivity and specificity. These techniques are useful for the early diagnosis of AD and lay a good foundation for further understanding of the underlying pathological mechanism [10]. According to the amyloid cascade hypothesis [5], in the preclinical state of AD, a large amount of amyloid is accumulated in the brain, and then neuronal degeneration occurs, but at this time, cognitive function has not changed. Although experimental studies have shown that Aβ impairs synaptic function, the results of neuroimaging are ambiguous [11, 12]. As the course of AD progresses, the cognitive function of the patients continues to decline. Studies have found that cognitive function decline is closely related to glucose metabolism in the frontal lobe and temporal parietal lobe [13]. The decline of cognitive function in AD patients is not related to the spatial distribution of Aβ load but is closely related to low glucose metabolism [14].

Therefore, the main purpose of this study is to investigate the characteristics of Aβ load and FDG metabolism in the brain of AD patients by PET technology using ^{18}F-AV45 and ^{18}F-FDG as markers, and assess the correlation between the PET imaging and cognitive impairment. Our results will provide a basis for establishing reliable bioimaging indicators for the early diagnosis of AD.

Methods

Patients

27 AD patients included in this study were inpatients of the Department of Neurology of the First Affiliated Hospital of Dalian Medical University from March 2014 to December 2019. The diagnosis of AD was made according to the criteria of NINCDS-ADRDA. All subjects underwent detailed medical history collection and clinical examination of the nervous system. Patients with the following conditions were excluded: 1) Clinical conditions that can cause progressive memory decline and cognitive dysfunction

including epilepsy, encephalitis, stroke, acquired immune deficiency syndrome, treponema pallidum infection, long-term use of drugs that cause cognitive dysfunction or alcoholism, vitamin B deficiency; 2) Hachinski Ischaemia Score (HIS) score > 4 points, Hamilton Anxiety Rating Scale (HAMA) score ≥ 7 points, Hamilton Depression Rating Scale (HAMD) score ≥ 7 points; 3) Those with severe heart, liver, lung, kidney and other organ diseases; 4) Those who cannot cooperate to finish the clinical physical examination and cognitive assessments; 5) Left-handed; 6) Subjects who could not lie down for 40 minutes. All patients and their legal guardians understood the purpose and content of the study and voluntarily signed an informed consent form. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University.

Neuropsychiatric assessments

The cognitive function of the AD patients was assessed with the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) scales by two fixed neurologists. MMSE scores (30 points in total score) < 27 points were considered as dementia, 21 to 26 points were mild, 11 to 20 points were moderate, and 0 to 10 points were severe dementia. The MoCA scores (30 points in total) < 26 points were considered as dementia.

Positron emission tomography

The PET-CT was the Biograph 64 PET/CT scanner (Siemens, Germany). ^{18}F-FDG imaging agent was automatically synthesized by ^{18}F-FDG drug synthesis system Explora FDG4 module by using Eclipse RD cyclotron (Siemens, Germany) and the radiochemical purity was > 95%. ^{18}F-AV45 imaging agent was synthesized by the Allinone module of Trasis company, prepared by the ^{18}F labeling of its corresponding precursor by the Department of Nuclear Medicine of the First Affiliated Hospital of Dalian Medical University. The final product's radiochemical purity was > 95%, and endotoxin and bacteria tests were negative, which met the requirements of radiopharmaceuticals.

All 27 AD patients underwent the ^{18}F-AV45 and ^{18}F-FDG PET examination within 2 weeks. For AV45 and FDG-PET data, a professional doctor in the Department of Nuclear Medicine used a blind method to visually analyze PET images to assess the radioactive distribution of the cerebral cortex. NeuroQ (version 3.7) is a commercial brain imaging analysis software tool that can be quantitatively analyzed by automatically quantifying the average pixel values in 47 standardized brain regions, and the average value between all pixels of the whole brain is used as a reference for standardization. By comparing with the 50 normal control groups without mental illness or symptoms in the standard database, the patients' brain FDG metabolism and Aβload changes in each brain area were evaluated.

Statistical methods

SPSS25.0 software was used to analyze the data. Normally distributed measure- ment data was expressed as mean±standard deviation (x±s), and non-normally distributed measurement data was expressed as median (quartile difference). Normally distributed measurement datas with equal variance

were tested by the independent sample T test. Datas that were not normally distributed were analyzed by the non-parametric test of two independent samples. Counting data used Fisher's exact probability method or Poisson regression. Pearson or Spearman correlation was used for correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Comparison of general data of patients with mild and moderate AD

There were 13 patients in the mild AD group, 14 patients in the moderate AD group. There was no statistically significant difference between the mild and moderate AD group in terms of age, gender, education level, and course of disease (Additional table 1, P values > 0.05). The difference in the MMSE and MoCA scores between the two group was statistically significant (Additional table 1, P value < 0.0001).

Comparison of distribution characteristics of Aβ in patients with mild and moderate AD

Preliminary visual analysis revealed that among 27 AD patients, 22 had visible Aβ load, accounting for 81.48%. Compared with patients with mild AD, the range and degree of Aβ load were not significantly different in moderate AD. However, there were 5 patients (2 mild and 3 moderate AD patients) with no Aβ load in the cerebral cortex (Figure 1).

NeuroQ software divided the cerebral cortex into 30 different functional brain regions according to the Anatomical Automatic Labeling (AAL) method. In the present study, we used the number of brain areas with increased AV45 deposition to indicate the extent of brain areas involved. It was found that moderate patients had an average increase of 0.87 brain region with increased AV45 deposition compared with mild patients, but the difference between the two was not statistically significant (Table 1, P value = 0.25).

Further comparing the degree of Aβ load in the frontal, temporal, parietal and occipital lobes, it was found that there was no statistically significant differences in the degree of Aβ load between the patients with mild and moderate AD (Additional table 2, P values > 0.05).

Correlation between Aβ load and cognitive impairment in AD patients

In order to explore the relationship between Aβ load and cognitive impairment in AD patients, we analyzed the correlation of the range and degree of Aβ load in the functional areas of the frontal, temporal, parietal, occipital lobes and the total score of the MMSE and MoCA scales and subtests scores of MoCA. The results showed that the range of Aβ load in the cerebral cortex was not correlated with the total scores of MMSE and MOCA (Table 2, P value > 0.05). While the degree of Aβ load of the left superior parietal lobe, the left associative visual cortex, and the right Broca area was negatively correlated with the language and abstract reasoning subtest of MoCA (Additional table 3, P values are 0.02, 0.04, and 0.04, respectively).

Comparison of FDG metabolism reduction in patients with mild and moderate AD

According to the preliminary visual analysis, 26 of the 27 AD patients had a decrease of FDG metabolism, accounting for 96.30%. Compared with mild AD patients, the range and degree of FDG metabolism reduction was significantly increased in moderate AD. Only one mild AD patient had no reduction of FDG metabolism, and there was no Aβ load in any brain areas of this patient (Figure 2).

We used the number of brain areas with reduced FDG metabolism to indicate the extent of brain areas involved. Comparing the range of reduced FDG metabolism in 30 brain functional areas, we found an increase of 1.83 brain regions in moderate AD patients compared with mild AD patients and the difference between the two was statistically significant (Table 1, P value < 0.001).

Further comparing the degree of FDG metabolism, we found that the FDG metabolism reduction in some brain functional areas were significantly increased in moderate AD patients (Table 3).

Correlation between decreased FDG metabolism and impaired cognitive function in AD patients

To explore the relationship between decreased FDG metabolism and cognitive impairment in AD patients, the correlation of reduced FDG metabolism in brain functional areas and the total score of MMSE or the total score and subtest scores of MOCA were analyzed.

The results showed that 1) The range of reduced FDG metabolism in the cerebral cortex was negatively correlated with the total scores of MMSE or MoCA (Table 2, P value < 0.05); 2) The degree of FDG metabolism in some brain functional areas was positively correlated with the total score of MMSE scale or MoCA scale (Table 4); 3) The correlation between the degree of FDG metabolism and subtests scores of MoCA were shown in Additional table 4.

Discussion

In recent years, neuroimaging techniques, such as CT and MRI, play important roles in AD diagnosis. While Aβ PET uses amyloid tracer to show the plaque load in the brain [15], FDG-PET shows the state of glucose utilization of the brain and indirectly reflects the neuronal function and neurodegeneration in AD patients [8]. The present study mainly explored the correlation of Aβ load, FDG metabolism reduction and cognitive impairment, which would provide a reliable bioimaging basis for the clinical diagnosis and assessment for AD patients.

The value of PET in the diagnosis of AD
In AD disease progress, changes in brain function are earlier than changes in imaging structure. Therefore, in the early stage of AD, before the structural imaging changes, functional imaging can detect the decline of cognitive function. By observing the changes of amyloid deposits and glucose metabolism in each brain lobe, we can not only improve the diagnosis rate of early AD, but also identify different types of dementia, such as frontotemporal dementia and vascular dementia [16]. ^{11}C-Pittsburgh compound B

(^{11}C-PIB) PET was the earliest and most used PET imaging technology for Aβ in the past, but the synthesis of ^{11}C-PIB was complicated and its half-life was short, while ^{18}F-AV45 had longer half-life and its specificity was high [17]. A study of ^{18}F-AV45 PET imaging of 184 patients found that about 76% of patients with AD had positive amyloid plaques, about 38% of MCI patients had AV45 retention in their brains, and 14% of normal people had AV45 retention, indicating that AV45-PET had a high sensitivity [18]. On the other hand, the most used PET imaging agent to mark glucose metabolism is ^{18}F-FDG, which can reflect the decline of neuronal function and the number of neurons in the brain. Bloudek et al. found that the sensitivity of FDG-PET for AD diagnose was 90%, and the specificity was 89% [19]. A study found that the accuracy of AD diagnosis could be improved to 90% when FDG-PET was used in combination with Aβ PET [20]. This study also found that 5 out of 27 AD patients had no amyloid plaques in ^{18}F-AV45 PET images, and 1 of these 5 patients showed no reduction in FDG metabolism. However, all these 5 patients met the NINCDS-ADRDA criteria for AD clinical diagnosis, indicating that clinical manifestation was not always compelling with the imaging changes.

Correlation of impaired cognitive function, Aβ load, and decreased FDG metabolism in AD patients

Neuroimaging studies found that Aβ deposition was negatively associated with cognitive impairment or brain metabolism in AD patients [21, 22]. However, another study showed that the correlation between Aβ load and cognitive impairment was weak [23]. Even more, several studies failed observe robust association between Aβ plaque counts and dementia severity [24]. A study with assessment of 456 brains found that the difference of AD pathological changes pathology between persons with and those without dementia decreased with increasing age. The association between Aβ plaques and dementia was strong at 75 years of age but reduced at 95 years of age [25]. Engler et al. found that Aβ load in the frontal lobe, parietal lobe, occipital lobe, and temporal lobe was significantly increased in AD patients compared with healthy controls. However, after 2-year follow-up, PIB-PET imaging showed no significant changes of Aβ load when compared with 2 years ago, while the MMSE score decreased overall, indicating that Aβ load was not obviously changed as cognitive function declined [23]. Hyman et al. also found that Aβ load did not change significantly as the disease progressed [24]. In present study, our results showed that the range of Aβ load did not show statistically significant differences between mild and moderate AD patients and the range and range of Aβ load were not related to the total scores of MMSE and MoCA.

On the other hand, AD patients show reduced glucose metabolism in specific brain regions, and as the disease worsens, the degree and the scope of reduced glucose metabolism are also increasing. Thus, FDG-PET can not only help to diagnose AD, but also reflect the disease progression. Knopman et al. found that the decline in glucose metabolism was an independent risk factor for AD and could predict the occurrence and development of AD. By improving glucose metabolism, the incidence of AD could be reduced, and the development of the disease could be effectively delayed [26]. Typical AD patients might have low metabolism in the temporal parietal lobe and posterior cingulate gyrus. And as the disease progressed, the frontal lobe might also be affected [27, 28]. And glucose metabolism in the frontal lobe and temporal parietal lobe was closely related to cognitive impairment [14]. Our study found that patients with moderate AD had a significantly increased range of reduced FDG metabolism compared with patients with mild AD, and moderate AD patients had lower glucose metabolism in some brain functional

areas. Moreover, we found that the degree of FDG metabolism in frontal lobe, temporal lobe, and parieto-temporal cortex was positively correlated with the total score of MMSE scale, suggesting that the cognitive impairment of patients was related to the decrease of glucose metabolism, mainly in the frontal lobe and temporal parietal lobe, which was consistent with previous studies. Lehmann et al. found that the cognitive decline in AD patients was related to low glucose metabolism, but not related to the spatial distribution of amyloid deposits [14].

Limitation

This study also had certain limitations: 1) No healthy control groups were included; 2) The sample size is relatively small in the present study.

Conclusion

By using ^{18}F-AV45 and ^{18}F-FDG PET imaging, we investigated the relationship of amyloid load, reduced glucose metabolism and cognitive impairment in AD patients. Our results showed that brain ^{18}F-AV45 and ^{18}F-FDG imaging might be potential biomarkers of AD, and ^{18}F-FDG imaging was correlated with the degree of cognitive impairment in AD patients. Our findings would provide a basis for early diagnosis of AD and lay a foundation for further in-depth studies of AD.

Abbreviations

^{11}C-PIB, ^{11}C-Pittsburgh compound B

^{18}F-AV45, ^{18}F-florbetapir

^{18}F-FDG, ^{18}F-Fluorodeoxyglucose

AAL, Anatomical Automatic Labeling

Aβ, β-amyloid

AD, Alzheimer's disease

HAMA, Hamilton Anxiety Rating Scale

HAMD, Hamilton Depression Rating Scale

HIS, Hachinski Ischaemia Score

MMSE, Mini-Mental State Examination

MoCA, Montreal Cognitive Assessment

NFT, neurofibrillary tangles

NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

PET, positron emission tomography

Declarations

Ethics approval and consent to participate

All patients and their legal guardians understood the purpose and content of the study and voluntarily signed an informed consent form. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University.

Consent for publication

All patients and their legal guardians understood the purpose and content of the study and voluntarily signed an informed consent form.

Availability of data and materials

All data generated or analysed during this study are included in this article and its supplementary information files.

Competing interests

All the authors have no conflict of interest to declare.

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Not applicable.

Authors' contributions

CD and YZ designed the project of this manuscript. JJ, LZ, JX, JC carried out all the clinical works. JJ, FZ, LZ, JX, JC, and RZ contributed to statistical analyses and results interpretation. JJ, FZ, JC, and RZ contributed to drafting of the manuscript. LZ, YZ, and CD revised the manuscript. CD contributed to research concept, research administration and support. All authors edited and approved the final version of the manuscript.

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Tables

Table 1. Comparison of the range of Aβ load and FDG metabolism in the brain of patients with mild and moderate AD

	Correlation coefficient [95%CI]	Standard deviation	Z value	P value
Aβ load	0.87[0.68, 1.11]	0.12	-1.16	0.25
FDG metabolism	1.83[1.40, 2.42]	0.14	4.33	0.000***

Note: ***P<0.001

Table 2. Correlation between the range of Aβ load or FDG metabolism and the total scores of MMSE or MoCA

	MMSE		MoCA	
	Correlation coefficient	P value	Correlation coefficient	P value
Aβ load	0.03	0.87	-0.05	0.80
FDG metabolism	-0.74	0.000***	-0.54	0.004**

Note:***P<0.001

Table 3. Comparison of the degree of FDG metabolism in the brain of patients with mild and moderate AD

Brain area	The degree of FDG metabolism		P value
	Mild AD	Moderate AD	
Left superior frontal gyrus	0.98±0.04	1.01±0.07	0.32
Left mid-frontal gyrus	1.11±0.04	1.08±0.06	0.14
Left inferior frontal gyrus	1.06±0.03	1.05±0.08	0.62
Left medial frontal gyrus	1.00±0.06	1.02±0.08	0.61
Left Broca area	1.15±0.04	1.10±0.07	0.04*
Left superior lateral temporal lobe	1.09±0.04	1.07±0.05	0.14
Left medial anterior temporal lobe	0.70(0.68,0.72)	0.72(0.69,0.73)	0.47
Left medial posterior temporal lobe	0.92±0.03	0.92±0.04	0.99
Left inferior lateral anterior temporal lobe	0.87±0.02	0.83±0.08	0.08
Left inferior lateral posterior temporal lobe	0.97(0.94,0.99)	0.90(0.84,0.96)	0.01*
Left superior parietal lobe	0.97(0.94,0.99)	0.99(0.96,1.00)	0.29
Left inferior parietal lobe	1.06±0.05	1.06±0.11	0.98
Left parieto-temporal cortex	1.05±0.05	0.99±0.07	0.02*
Left associative visual cortex	1.09±0.04	1.06±0.06	0.14
Left primary visual cortex	1.19±0.07	1.23±0.10	0.24
Right superior frontal gyrus	1.01±0.04	1.00±0.06	0.67
Right mid-frontal gyrus	1.12(1.09, 1.13)	1.07(1.04, 1.14)	0.09
Right inferior frontal gyrus	1.09±0.04	1.05±0.07	0.14
Right medial frontal gyrus	1.05(1.01, 1.07)	1.06(1.02, 1.08)	0.63
Right Broca area	1.12±0.04	1.07±1.00	0.09
Right superior lateral temporal lobe	1.07±0.05	1.03±0.07	0.15
Right medial anterior temporal lobe	0.70±0.03	0.70±0.04	0.93
Right medial posterior temporal lobe	0.88±0.02	0.88±0.02	0.85
Right inferior lateral anterior temporal lobe	0.87±0.04	0.82±0.07	0.03*
Right inferior lateral posterior temporal lobe	0.94±0.05	0.86±0.07	0.004**
Right superior parietal lobe	0.98±0.05	1.01±0.05	0.08
Right inferior parietal lobe	1.03±0.05	1.06±0.09	0.28
Right parieto-temporal cortex	1.02±0.06	0.97±0.09	0.09
Right associative visual cortex	1.06±0.02	1.00±0.07	0.01*
Right primary visual cortex	1.15±0.07	1.17±0.09	0.58

Note：*P＜0.05；**P＜0.01

Table 4. Correlation between the degree of FDG metabolism and the total score of MMSE or MoCA in brain functional areas

	Area	Correlation coefficient	P value
FDG metabolism and MMSE score	Left inferior lateral posterior temporal lobe	0.51	0.01*
	Left parieto-temporal cortex	0.42	0.03*
	Right mid-frontal gyrus	0.45	0.02*
	Right Broca area	0.39	0.046*
	Right inferior lateral anterior temporal lobe	0.50	0.01*
	Right inferior lateral posterior temporal lobe	0.67	0.000***
	Right parieto-temporal cortex	0.43	0.02*
	Right associative visual cortex	0.57	0.002**
FDG metabolism and MoCA score	Left inferior lateral posterior temporal lobe	0.46	0.02*
	Left parieto-temporal cortex	0.38	0.0499*
	Right inferior lateral posterior temporal lobe	0.46	0.02*
	Right associative visual cortex	0.50	0.01*

Note：*P＜0.05；**P＜0.01；***P＜0.001

Figures

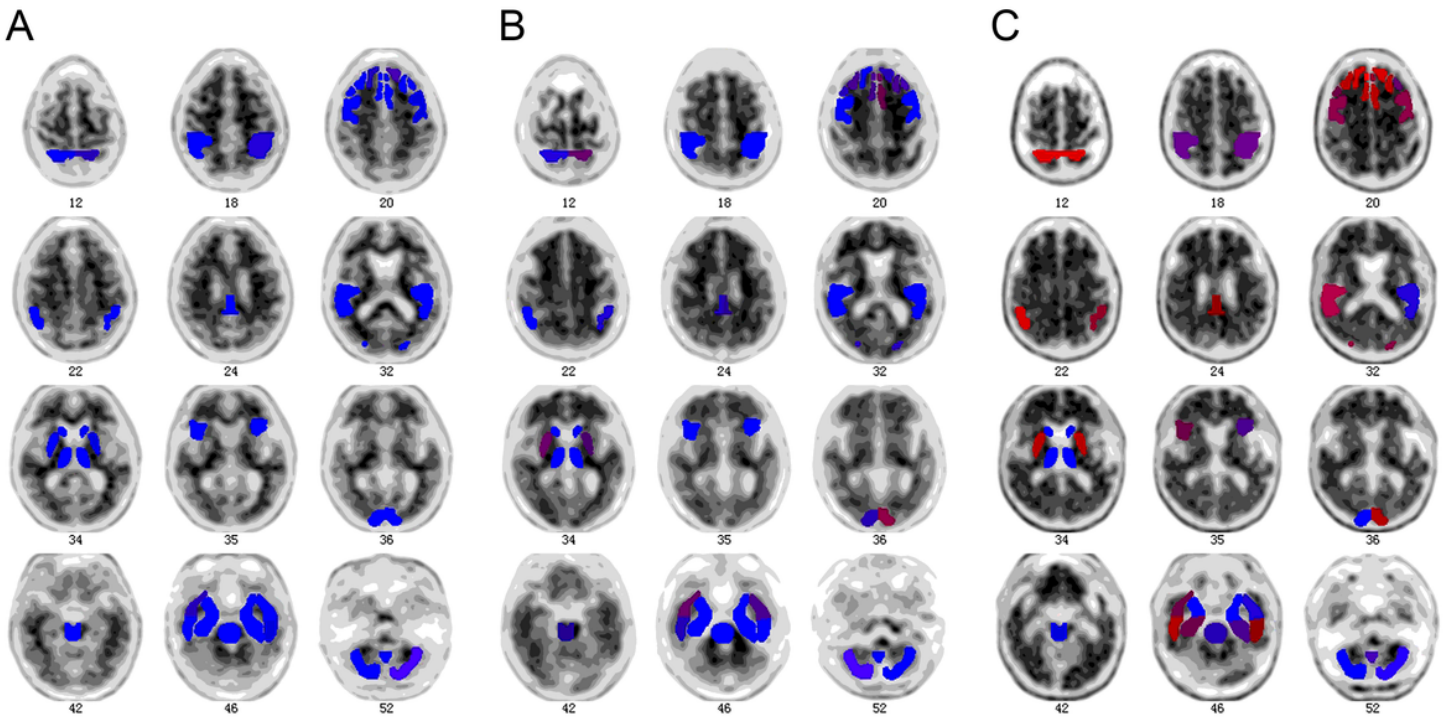

Figure 1

Representative images of Aβ load visual analysis data in AD patients. A. AV45-PET images with no Aβ load; B. AV45-PET images with mild Aβ load; C. AV45-PET images with obvious Aβ load. Red color means

more Aβ load and blue color means less Aβ load.

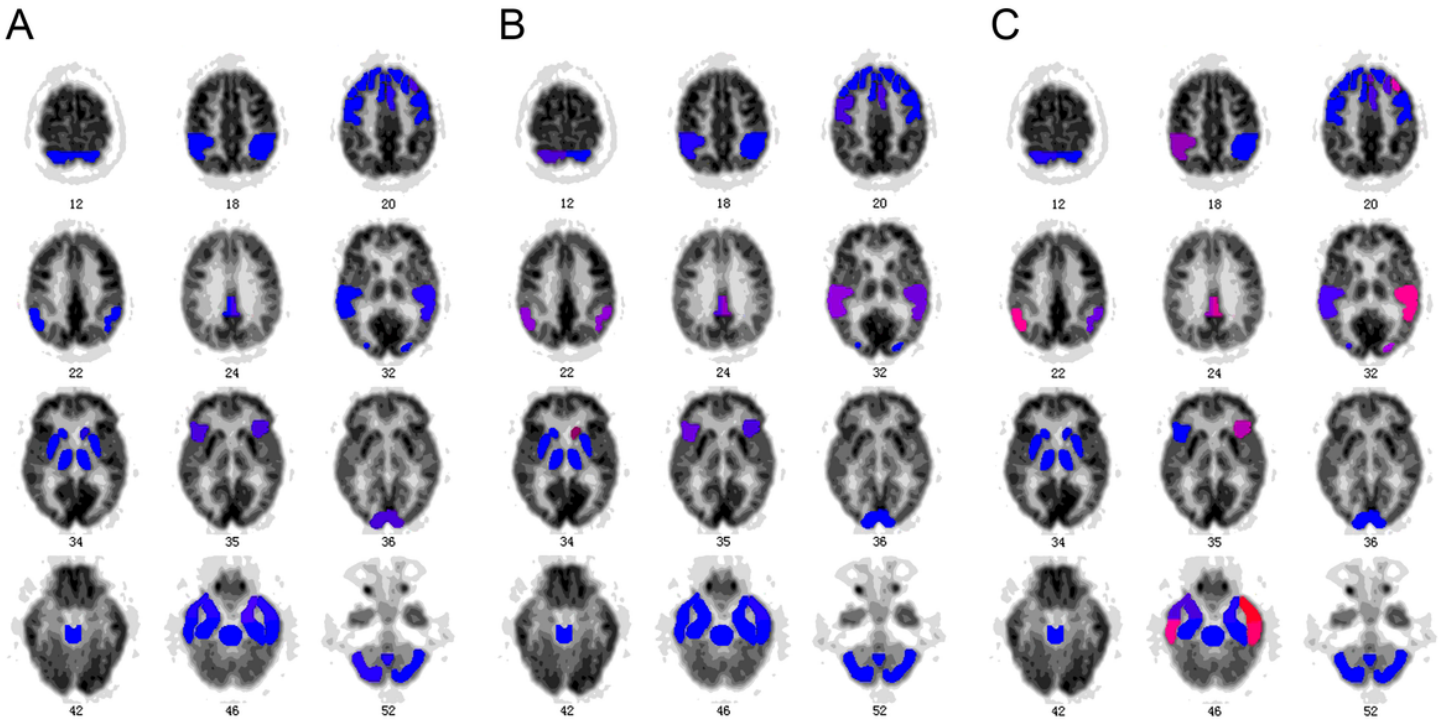

Figure 2

Representative images of FDG metabolism visual analysis data in AD patients. A. FDG-PET images with no FDG metabolism reduction; B. FDG-PET images with mild FDG metabolism reduction; C. FDG-PET images with obvious FDG metabolism reduction. Red color means more reduction of FDG metabolism.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.png
- TableS2.png
- TableS3.png
- TableS4.png