Clinical Applications of PET-MRI Technique in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD), a neurodegenerative disease that afflicts many people as the most common form of dementia, still lacks effective symptomatic treatments. PET-MRI hybrid imaging technology combines Positron emission tomography (PET) and Magnetic resonance imaging (MRI), which is believed to be helpful for the early screening, diagnosis, disease course monitoring and treatment evaluation of AD, and has a very promising technical prospect. This review reviews the roles of PET and MRI in the diagnosis and monitoring of AD, respectively, and analyzes their advantages and disadvantages. Later, based on previous studies, this review discusses the effects of the two technologies when they are used together, and compares them with each other and PET-Computed Tomography (CT) hybrid imaging technology respectively, indicating that PET and MRI can complement each other and give full play to their respective advantages. After this, the review also discusses the problems and challenges still faced by this hybrid imaging technology. This paper presents the current research status and future research direction of PET-MRI for AD diagnosis and monitoring, which is of great value to its research and application

Keywords: Alzheimer's Disease, PET, MRI, Hybrid Imaging Technology.

1. Introduction

As an irreversible brain disease, AD will cause progressive impairment of memory and cognitive ability and dementia in the aged. Patients with AD may show memory loss, followed by disorientation, judgment disorder, inattention, aphasia, apraxia, agnosia and dyslexia, and mood changes show depression, indifference, easy to anger, paranoia and other symptoms [1]. These patients may also have signs of extrapyramidal involvement such as the grip and sucking reflex, significantly reduced movement, unsteady gait, reduced stride length, increased muscle tone, and reduced movement.

Despite partial success in symptomatic AD treatment, previous studies have shown that a single therapy for AD is unlikely. There is currently no very effective specific therapy [2]. In AD patients' brains, metabolic alterations in amyloid precursor proteins lead to the developing of amyloid plaques in the cortex and limic system, while changes in the microtubule-associated protein tau led to the development of neurofibrillary tangles, which are pathological features of patients with AD [3].

PET is a nuclear medicine method that measures the cells' metabolic activity in human tissue, helps visualize biochemical changes occurring in the body, and detect metabolism within body tissues. In addition to detecting the distribution pattern of radioactive drugs, it also has a quantitative function, whose results can be used in treatment decision-making [4]. PET works by connecting radioactive atoms to chemicals that a certain organ or tissue naturally uses throughout its metabolism to create radionuclides, which are made by attaching radioactive atoms to chemicals that a particular organ or tissue naturally uses during its metabolism. For example, adding a radioactive atom to glucose produces fluorodeoxyglucose (FDG). Because glucose is important for brain metabolism, FDG-PET is widely used to diagnose AD. Amyloid brain PET looks for amyloid plaques and tau tangles by injecting patients with "tracer" molecules that stick to amyloid plaques and visualize their location in the brain. PET can detect amyloid beta (Aβ) deposition, tau protein accumulation, microglia activation and neuroinflammation in AD patients, and is mainly used for early diagnosis of patients.

MRI is a process in which hydrogen atoms are excited by a radio-frequency pulse in a strong external magnetic field. A computer then integrates the magnetic resonance phenomenon without ionizing radiation and invasiveness. This technique has high soft tissue resolution and multi-plane

imaging capability [5]. MRI can monitor the course of AD by detecting hippocampal atrophy, gray matter loss, and cerebrospinal fluid changes.

A combined imaging method that has gained popularity is PET-CT. The fundamental idea behind PET-CT is to first introduce radionuclides for imaging before combining that with CT anatomy for diagnosis. Metabolites, glucose, amino acids, proteins, peptides, and other substances have all been used as major imaging agents.

PET-MRI can image disease cells as they spread through tissue. The system can collect PET and MR Images to obtain disease marker molecule information and histological information. At the same time, combining these two technologies combines the advantages of PET for early diagnosis of AD with the advantages of MRI for course monitoring. It has higher sensitivity and specificity than PET-CT, so it has a high research value. However, the current application of PET-MRI is far from widespread because there are still many outstanding issues. For example, the conditions required for the two technologies may interact with each other, which may reduce the accuracy of the detection and increase the requirements for the materials used in the instrument, which may increase the required cost. These challenges should lead to more research in the future, which will drive the diagnosis together with the monitoring of AD.

2. PET and MRI in Alzheimer's disease

2.1. PET in Alzheimer's disease

To diagnose and to treat AD patients, PET can detect Aβ deposition, tau protein accumulation, microglial activation and neuroinflammation [6], which is usually used to study brain glucose metabolism, various neurotransmitter systems, neuroinflammation and protein aggregation characteristic of disease [7]. PET is a common technique for AD because it reveals pathophysiological processes different from the normal ageing process [8]. Therefore, PET plays an important role in early screening, diagnosis, course monitoring and treatment evaluation of AD.

FDG-PET evaluates the patterns of glucose metabolism in several brain areas, identifying those with poor metabolism. In comparison to other diagnostic techniques like clinical guidelines, computed tomography, single photon emission computed tomography, etc., recent studies show that FDG-PET approaches high standards in terms of sensitivity and specificity when used to diagnose AD [8]. Reduced glucose metabolism was found in the precuneus, inferior parietal lobule, middle temporal gyrus, and posterior cingulate cortex in AD patients. In mild cognitive impairment patients, studies show that glucose metabolism is reduced only in Posterior cingulate cortex [9]. Therefore, FDG-PET can be used as an early AD marker for conversion from mild cognitive impairment to AD. At the same time, more studies show that different hypometabolic regions in the brain identified by FDG-PET provide support for the differentiation of Alzheimer's disease from other causes of dementia, such as frontotemporal dementia and dementia with Lewy bodies. For instance, in patients with temporal lobe neurosis, glucose hypometabolism is more common in the frontal, anterior cingulate, and anterior temporal regions. In contrast, patients with AD had a higher prevalence of hypometabolism in the temporoparietal and posterior cingulate regions [10]. Through real-time monitoring of alterations in glucose metabolism, FDG-PET is also an effective marker for tracking the course of AD.

Aβ deposition is considered the precursor of AD's cognitive symptoms, plays an important role in the pathogenesis, and is also an important marker of AD [11,12]. Amyloid brain PET measures Aβ deposition by different amyloid chromogenic agents, such as [11C]-Polyisobutylene. It has been demonstrated that [11C]-Polyisobutylene selectively binds synthetic A-40 and A-42 fibers as well as insoluble A plaques including A-40 and A-42 in AD brain [13,14]. Contrarily, [11C]-Polyisobutylene does not bind to soluble A substantially and most likely does not bind to nonfibrillar plaques or oligomeric forms of A until they reach a critical size (which has not yet been established) [15]. Due to the relatively low SP value of amyloid, amyloid PET imaging must be done in patients with clinically suspected AD. However, PET amyloid beta imaging agents can still support the clinical

assessment of severe cognitive impairment and offer objective markers for AD pathology [11]. Studies show that the changes in amyloid deposition detected by amyloid brain PET are consistent with the results of aβ deposition sequence in different brain regions of AD patients found at autopsy [16-18]. So amyloid brain PET can also quantitatively measure the amyloidosis of AD in vivo, track its longitudinal process, and provide a judgment basis for monitoring the course of the disease and evaluating anti-amyloid beta therapy of patients [7].

2.2. MRI in Alzheimer's disease

Early studies show that voxel information carried by germinal-matrix and white matter tissues [19], hippocampus atrophy under the influence of early tau pathology in the disease process of AD, etc., can be used as features to distinguish AD patients from healthy subjects by MRI.

So far, the early diagnosis of AD based on MRI is still difficult. Although some studies show that the application of unbiased clustering of MRI data in the diagnosis of Alzheimer's disease has a certain prospect [20], the effect of this method in the selection of homogenous patient groups in clinical trials is higher than that in the early diagnosis of Alzheimer's disease because of the high accuracy requirement of this method [21].

MRI-based assessment of brain atrophy is considered an effective method to stage the disease and assess the progression of AD. A model classifies four different stages of AD based on MRI results - non-dementia, very mild dementia, mild dementia and moderate dementia [22]. This staging may aid in the early discovery of AD, the monitoring of disease development, and the evaluation of therapy efficacy.

There are two main building blocks in classical MRI-based AD automated diagnostic systems -- extracting features/biomarkers from MRI data and classifiers based on these features/biomarkers. The following are three main AD feature extraction techniques:

First，the voxel-based approach. Voxel intensity is used as a classification feature, for example, to measure the density of local tissues of the brain (i.e., white matter, gray matter, and cerebrospinal fluid) [23,24]. The results obtained by this method are simple and intuitive, but its high-dimensional features often lead to over-fitting of information and a lack of regional details.

The second technique is the region of interest (ROI)-based approach. Based on specific hypotheses regarding defective brain regions, such as evaluations of cortical thickness, gray matter volume, and hippocampus volume [25,26]. Although the full brain is covered by this technology and the feature dimension is minimal, it is simple to overlook subtle pathological alterations.

Another popular method of feature extraction is patch-based approach. Small regions of the entire brain image are segmented, and from these patches, feature vectors are extracted. This method can capture subtle changes in the brain with significantly reduced dimensionality, but it is difficult to screen informative patches [22].

2.3. PET-MRI in Alzheimer's disease

Before PET-MRI, there was another popular system for diagnosing AD, PET-CT. Even though PET-CT is substantially more expensive than PET alone, its advantages have led to it replacing PET within a few years. For example, scanning time is significantly shortened, flux is increased, and full 3D image acquisition is possible. The success of PET-CT has led researchers to consider other hybrid systems. Because PET/CT is usually supplemented by MRI, some studies consider using MRI instead of CT technology to form a hybrid system with PET [27]. MRI generally offers superior soft tissue contrast to CT, has higher sensitivity and specificity, and does not expose the patient to ionizing radiation, all of which are significant benefits. Furthermore, the Lorentz force, which can reduce the positron distribution range and enhance the resolution of the position determination of radionuclides by PET, occurs in the strong magnetic field produced by MRI, demonstrating the complimentary nature of the two technologies. In the early diagnosis of AD, hippocampus atrophy and cerebrospinal fluid, two of the most important imaging markers, can be detected by MRI, and its detection targets also include arterial spin markers and cerebral blood flow. For an early diagnosis of AD, PET

measures changes in the brain's glucose metabolism, changes in the amount of A42 in the cerebrospinal fluid, and changes in the amount of A tracer in the brain. Clinically, PET and MRI may also be utilized to differentiate AD from other dementias. PET can distinguish between AD and frontotemporal degeneration, while MRI can tell vascular dementia from dementia with lewy bodies apart. The combination of images obtained by the two technologies is more conducive to monitoring the disease course of AD [28]. Suppose the hybrid PET-MRI technology can be realized. In that case, the molecular and functional information of PET can be combined with the image acquisition ability of MRI for soft tissue comparison, which has an exciting research prospect.

However, the development of hybrid PET-MRI systems faces some problems. Inserting a PET detector into an MRI scanner may affect the scanner's static magnetic and radiofrequency fields and cause gradient defects in the MRI image. The MRI scanner itself has a uniform magnetic field, and superconducting magnets usually have a uniformity of one part per million to ensure that the proton resonates at the same frequency. Adding a PET detector reduces the uniformity of the static magnetic field and results in image artifacts. The effect on the RF field is caused by electromagnetic interference. Since MRI detects low-intensity signals, it is more susceptible to electromagnetic signal interference caused by adding PET, which we do not want to detect. The PET component, which is an additional piece of hardware in the gradient coil of the MRI instrument, alters the system's MRI eddy current properties, potentially leading to a lengthened switching time and spatial linear degradation. As a result, the fundamental imaging performance is impacted, along with the spatial resolution, scanning speed, and picture uniformity. MRI may also affect the work of PET. Because magnetic fields can affect the trajectories of electrons, making the pulses defocus in space and time, the photomultiplier tubes inside PET do not work properly in the strong magnetic fields of MRI scanners. At the same time, changes in magnetic fields can induce eddy currents in PET electronics. All these will interfere with the PET signal analysis [29].

With the latest research, some problems hybrid systems faces have been solved. In other investigations, fiber optics are used to keep PET electrons away from the magnetic field and prevent interference between MRI and PET [30]. The quality of the PET imaging itself, however, can be compromised by light loss along the fiber. In further research, readout electrons near or inside the magnetic field of a standard MR scanner were directly coupled with using very short fibers or scintillating crystals [31]. These methods retain the pmt because of its strong signal amplification capability and stability. Another solution is to replace the pmt with another solid-state component, namely, to build a magnetically insensitive PET detector [30]. In addition to improving the equipment, another research direction is to design attenuation correction system, because MR Image does not reflect the direct photon attenuation information, it is necessary to find a reliable alternative standard to correct the PET data. Examples include piecewise 2-point Dixon MR Imaging sequences, ultra-short echo time sequences, atlas-based methods, machine learning methods, PET/MR Imaging systems using time of flight technologies, and the utilization of non-MR data. PET-MRI has been gradually put into the detection of tumors, and for the diagnosis and monitoring of AD, based on these technical advances, there is still a lot of room for improvement of the PET-MRI hybrid system. It can be put into clinical use in large quantities when the technical level is perfected and accurate, and the cost is affordable.

3. Discussion

FDG-PET can detect differences in glucose metabolism in the brain, and amyloid brain PET detects amyloid deposition, which can be able to be used for early diagnosis and identification of AD and also play an auxiliary role in monitoring the course of AD. MRI scans the brain for differences in voxel strength, abnormal structural areas (such as hippocampal atrophy), and other brain changes.

Using the hybrid PET-MRI imaging technology, most of the biomarkers in the clinical diagnosis of AD is able to be determined by combining the indicators that PET and MRI technology can detect. It combines the advantages of two technologies, namely, the ability of PET to analyze the metabolic

situation and substance composition in the brain and the ability of MRI to acquire 3D images. In this way, researchers can obtain both the molecular and metabolic information from PET and the anatomical and functional information provided by MRI. Compared with the already widely used PET-CT, it has improved the ability to compare soft tissues with higher accuracy. Based on previous research, PET is mainly used for early diagnosis of the disease, while MRI plays a significant role in monitoring the course of the disease in later stages, and the two technologies have different advantages in distinguishing AD from other dementias. Therefore, the combination of PET and MRI can obtain more comprehensive information and provide more reliable conclusions at all stages of the disease.

Mature PET-MRI will have a very wide range of applications. Based on its reliable and comprehensive conclusions, it can replace PET-CT to become an important tool in clinical screening, diagnosis, disease course monitoring and efficacy analysis for AD, advance the time of disease detection, identify dementia with similar symptoms, obtain accurate detection results, and seek the most effective treatment means. In addition, this technology will continue to promote the study of AD, including biomarker detection, animal model construction, drug development, etc. To be sure, PET-MRI worth researching and exploring.

The direct combination of two single technology can cause a series of problems. The addition of PET detectors can alter the magnetic and radiofrequency fields of the MRI itself, affecting the imaging results. However, the original PET detector materials cannot work properly under the high magnetic field intensity brought by MRI. Therefore, building a hybrid system of the two is still difficult to make them work simultaneously. This means replacing more suitable materials, designing proper structures to avoid this interaction, and designing proper correction systems to fine-tune the data. PET-MRI is already being used in other clinical applications, such as tumor detection. But identifying tissue in the brain is more difficult than bone or muscle, requiring greater accuracy, and better fixation of the subject’s head is a matter of constant improvement.

Further development of PET-MRI technology should focus on improving accuracy and shortening detection time. The main way to improve accuracy is to minimize the impact of the two detection systems on each other and maximize their functionality. You can also rule out outside influences, including temperature and the patient's state. To shorten the detection time, synchronous detection can be used instead of sequential detection. At the same time, due to the longtime of MRI, methods should be sought to shorten the self-detection time of MRI.

In conclusion, PET-MRI technology still needs continuous improvement and progress, which requires more research and practice. However, these investments are valuable and have an important role in promoting the diagnosis, screening, course monitoring and follow-up research of Alzheimer’s disease.

4. Conclusions

In conclusion, Alzheimer's disease is a long-standing problem in both scientific research and clinical treatment, and there is still no specific drug and treatment to cure it. Therefore, screening and course monitoring of AD are particularly important. More accurate, intuitive and low-cost detection technologies are needed and constantly improved. PET uses radionuclide imaging and MRI to detect electromagnetic waves, which are effective means to detect AD at this stage. PET-MRI is considered as a promising hybrid imaging technique. It combines the soft tissue resolution of MRI with the molecular and metabolic results of PET, and also preserves the advantages of PET and MRI for early screening and late detection, respectively. Therefore, compared with PET and MRI, it can diagnose and monitor the whole process of Alzheimer's disease more comprehensively and accurately, with higher confidence. PET-CT, a widely used hybrid technology, is more accurate and has more room for future development. At present, there are still many technical problems worth studying, mainly focusing on how to eliminate the mutual interference between the two technologies. The solution of these problems will further play the respective advantages of PET and MRI, improve the accuracy,

shorten the detection time and reduce the detection cost, so that PET-MRI can be widely used in experimental research and clinical treatment standards. In contrast, the development of PET-MRI technology can also make the research process more accurate and simpler and make clinical detection more convenient and reliable. As a result, the improvement will facilitate the development of AD research in the laboratory and the diagnosis, treatment and course monitoring of AD during clinical treatment.

References

[1] LANCTÔT K L, AMATNIEK J, ANCOLI-ISRAEL S, et al. Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms [J]. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2017, 3(3): 440–449.

[2] MANGIALASCHE F, SOLOMON A, WINBLAD B, et al. Alzheimer's disease: Clinical trials and drug development [J]. The Lancet Neurology, 2010, 9(7): 702–716.

[3] LÓPEZ O L, DEKOSKY S T. Clinical symptoms in Alzheimer's disease [G]//Dementias. Elsevier, 2008: 207–216.

[4] BEUTHIEN-BAUMANN B. PET-Basics [J]. Der Radiologe, 2018, 58(5): 487–500.

[5] VAN GEUNS R-J M, WIELOPOLSKI P A, DE BRUIN H G, et al. Basic principles of magnetic resonance imaging☆ [J]. Progress in Cardiovascular Diseases, 1999, 42(2): 149–156.

[6] VALOTASSIOU V, MALAMITSI J, PAPATRIANTAFYLLOU J, et al. SPECT and PET imaging in Alzheimer's disease [J]. Annals of Nuclear Medicine, 2018, 32(9): 583–593.

[7] NORDBERG A, RINNE J O, KADIR A, et al. The use of PET in Alzheimer disease[J]. Nature Reviews Neurology, 2010, 6(2): 78–87.

[8] BLOUDEK L M, SPACKMAN D E, BLANKENBURG M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in alzheimer's disease [J]. Journal of Alzheimer's Disease, 2011, 26(4): 627–645.

[9] MOSCONI L, TSUI W H, HERHOLZ K, et al. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, alzheimer's disease, and other dementias [J]. Journal of Nuclear Medicine, 2008, 49(3): 390–398.

[10] FOSTER N L, HEIDEBRINK J L, CLARK C M, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease[J]. Brain, 2007, 130(10): 2616–2635.

[11] MARCUS C, MENA E, SUBRAMANIAM R M. Brain PET in the diagnosis of alzheimer's disease [J]. Clinical Nuclear Medicine, 2014, 39(10): e413–e426.

[12] JOHNSON K A, MINOSHIMA S, BOHNEN N I, et al. Update on appropriate use criteria for amyloid PET imaging: Dementia experts, mild cognitive impairment, and education [J]. Alzheimer's & Dementia, 2013, 9(4).

[13] IKONOMOVIC M D, KLUNK W E, ABRAHAMSON E E, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease [J]. Brain, 2008, 131(6): 1630–1645.

[14] SVEDBERG M M, HALL H, HELLSTRÖM-LINDAHL E, et al. [11C] PIB-amyloid binding and levels of Aβ40 and Aβ42 in postmortem brain tissue from Alzheimer patients [J]. Neurochemistry International, 2009, 54(5–6): 347–357.

[15] VLASSENKO A G, BENZINGER T L S, MORRIS J C. PET amyloid-beta imaging in preclinical Alzheimer's disease [J]. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2012, 1822(3): 370–379.

[16] CLARK C M, PONTECORVO M J, BEACH T G, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: A prospective cohort study [J]. The Lancet Neurology, 2012, 11(8): 669–678.

[17] CLARK C M. Use of Florbetapir-PET for Imaging β-Amyloid Pathology [J]. JAMA, 2011, 305(3): 275.

[18] BARTHEL H. Switching on brain PET to light up amyloid pathology in vivo (perspective on "in vivo imaging of amyloid deposition in alzheimer disease using the radioligand 18F-AV-45 (florbetapir F 18)" J nucl med. 2010; 51:913–920) [J]. Journal of Nuclear Medicine, 2020, 61(Supplement 2): 227S-235S.

[19] CASANOVA R, WHITLOW C T, WAGNER B, et al. High dimensional classification of structural MRI alzheimer?s Disease data based on large scale regularization [J]. Frontiers in Neuroinformatics, 2011, 5.

[20] LEE S, VIQAR F, ZIMMERMAN M E, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network [J]. Annals of Neurology, 2016, 79(6): 929–939.

[21] COULTHARD E, KNIGHT M. Refining Alzheimer's disease diagnosis with MRI [J]. Brain, 2017, 140(3): 524–526.

[22] ISLAM J, ZHANG Y. Brain MRI analysis for Alzheimer's disease diagnosis using an ensemble system of deep convolutional neural networks [J]. Brain Informatics, 2018, 5(2).

[23] ASHBURNER J, FRISTON K J. Voxel-Based morphometry—the methods [J]. NeuroImage, 2000, 11(6): 805–821.

[24] KLOPPEL S, STONNINGTON C M, CHU C, et al. Automatic classification of MR scans in Alzheimer's disease [J]. Brain, 2008, 131(3): 681–689.

[25] ZHANG J, LIU M, LE AN, et al. Alzheimer's disease diagnosis using landmark-based features from longitudinal structural MR images [J]. IEEE Journal of Biomedical and Health Informatics, 2017, 21(6): 1607–1616.

[26] DUBOIS B, CHUPIN M, HAMPEL H, et al. Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease [J]. Alzheimer's & Dementia, 2015, 11(9): 1041–1049.

[27] FRAUM T J, FOWLER K J, MCCONATHY J. PET/MRI: [J]. Academic Radiology, 2016, 23(2): 220–236.

[28] ZHANG X Y, YANG Z L, LU G M, et al. PET/MR imaging: new frontier in alzheimer's disease and other dementias[J]. Frontiers in Molecular Neuroscience, 2017, 10.

[29] MUZIC R F Jr, DIFILIPPO F P. Positron emission tomography-magnetic resonance imaging: Technical review [J]. Seminars in Roentgenology, 2014, 49(3): 242–254.

[30] HERZOG H. PET/MRI: Challenges, solutions and perspectives [J]. Zeitschrift für Medizinische Physik, 2012, 22(4): 281–298.

[31] BINDSEIL G A, GILBERT K M, SCHOLL T J, et al. First image from a combined positron emission tomography and field-cycled MRI system [J]. Magnetic Resonance in Medicine, 2011, 66(1): 301–305.