REVIEW ARTICLE

Effectiveness of Contrast Agents and Molecular Indicators in Alzheimer's Diagnosis through PET and SPECT Imaging on Animal Models: A Systematic Scoping Review

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Abstract

Purpose: The importance of cognitive decline has increased due to population aging and lifestyle changes. A definitive diagnosis of Alzheimer's Disease (AD) is made only by postmortem histopathological examination, but in vivo imaging advances this diagnosis. The disease is associated with neuropathological features such as amyloid β (Aβ) plaques and Neurofibrillary Tangles (NFT) in the brain. The usefulness of contrast agents and compounds, such as SPECT and PET imaging, for the early identification of AD is investigated in this systematic scoping review. SPECT has been studied because it can yield reliable findings quickly, detect traces in data, and can link and evaluate the metabolism of mud and PET at high spatial resolution. The efficiency of molecular markers like tau protein, Translocator Protein (TSPO), and Amyloid β (Aβ), as well as contrast agents like [^{18}F] fluorodeoxyglucose and [^{11}C] acetate. Early detection and diagnosis of AD is very important, but current research on the effectiveness of contrast agents and molecules is limited. To address this gap, we conducted a systematic scoping review on PET and SPECT imaging to evaluate the role of these factors and indicators in the diagnosis of this disorder.

Materials and Methods: A systematic search was conducted on August 30, 2023, in PubMed, using the PRISMA guidelines, without any time or language restrictions. The search was limited to PubMed because it is a comprehensive and extensive database in the medical sciences and the number of results we found there was sufficient. Three independent reviewers screened the studies based on criteria, and relevant data from the included articles were extracted and analyzed.

Results: As a result of the initial search, 172 original articles were included in the study. Finally, data from 116 studies were extracted. The most used contrast agents were [^{18}F] fluorodeoxyglucose and its derivatives, [^{11}C] acetate, and chemicals based on iodine, respectively. The most often employed transgenic mouse strains in the studies were APP/PS1 and 5XFAD. On average, 23 animals were used in each study. Respectively, Amyloid beta, Tau protein, Translocator Protein (TSPO), Acetylcholinesterase (AChE), Monoamine Oxidase B (MAO-B), and Gonadotropin-Releasing Hormone Receptor (GnRHR) were identified the most as biomarkers in studies.

Conclusion: The study on PET and SPECT imaging for diagnosing AD has limitations, including the use of animal models and not evaluating the long-term effects or safety of contrast agents. Further research is needed to confirm these findings in clinical settings and assess the long-term impact of these contrast chemicals.

Keywords: Alzheimer's Disease; Single Photon Emission Computed Tomography; Positron Emission Tomography; Contrast Agents, Molecular Indicators.

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1. Introduction

The documentation of Alzheimer's Disease (AD) dates back to the early 20th century when Alois Alzheimer first recorded its existence. It is the main cause of neurodegenerative dementia [1]. There is now widespread recognition of these three stages of Alzheimer's disease: preclinical, mild cognitive impairment, and dementia [2-4]. Even though that not everyone with mild cognitive impairment will develop AD, research has shown a yearly progression rate of around 10-15% towards dementia [5]. AD dementia is characterized by a progressive decline in cognitive ability in several domains, resulting in impaired performance at work or in daily tasks [3]. A recent study indicates that there is a global population of around 416 million persons who are affected by AD dementia, prodromal AD, and preclinical AD dementia. Among the whole population, around 32 million individuals are explicitly diagnosed with AD dementia [6]. This condition is distinguished by the presence of aberrant proteins that, when seen by histological examination, take the shape of plaques known as senile or amyloid plaques. The plaques, consisting of beta-amyloid (Aβ) deposits, are located extracellularly. Additionally, neurofibrillary tangles, also known as NFTs, are seen in cells. These tangles are made up of clusters of hyperphosphorylated tau protein. Abnormal protein accumulation is linked to several metabolic processes including inflammation, oxidative harm, and lysosomal dysfunction [1, 7]. Accurately diagnosing AD, especially in its first phases, is a complex task that requires a comprehensive evaluation of the patient's medical background and a battery of neuropsychological tests. Dementia, including AD, may be diagnosed with the use of these tests, which also help to distinguish AD from other forms of dementia [1, 7]. There isn't a clear way to quantify how many functioning neurons are left in the brains of live people with AD right now. The illness is conclusively diagnosed by postmortem examination of brain tissue. According to the amyloid cascade theory, at least ten years must pass before clinical symptoms appear [8]. Therefore, it is crucial to investigate novel approaches for the early and accurate in vivo detection of AD to guarantee the effectiveness of treatments. Alzheimer's diagnosis methods are divided into traditional and new methods. Traditional techniques such as clinical assessment and medical history (expert interview with the patient and review of patient records [3]), imaging techniques, cognitive assessments and new techniques including biomarkers and cerebrospinal medical analysis, targeted Positron Emission Tomography (PET) imaging, biomarkers based on liquid biopsy and neuroimaging techniques and machine algorithms [9]. Among these methods, molecular neuroimaging methods for AD diagnosis, including PET and Single-Photon Emission Computed Tomography (SPECT), show more potential. Due to our molecular insight in this review as well as the success rate of nuclear medicine modalities in AD, our focus is on this method and other methods were not investigated in this study. Table 1 presents factors such as specificity range, sensitivity range, advantages,

Table 1. Comparison of Alzheimer's disease diagnostic tools [1-15]

Diagnostic tool	Type	Traditional/novel	Sensitivity range	Specificity range	Advantages	Challenges
Brain imaging techniques	Neuroimaging	Traditional	PET (amyloid): 70-90%, MRI: 85%	PET (amyloid): 90-95%, MRI: varied	Molecular insights	High cost, radiation exposure
Cognitive assessment	Clinical	Traditional	60-85%	70-85%	Patient history insights	Subjectivity, cultural bias
CSF analysis	Biomarkers	Novel	85-90%	90-95%	Disease-specific	Invasive, discomfort
Machine learning	Algorithm-based	Novel	80-90%	85-90%	Data pattern recognition	Data quality, interpretability
Blood-based markers	Biomarkers	Novel	70-80%	80-90%	Non-invasive early-stage diagnosis	Validation, variability

and challenges for traditional and new techniques. Functional neuroimaging methods like SPECT and PET are used in AD research to examine metabolic and biochemical alterations in the brain. These methods have been beneficial in acquiring insights into the underlying pathophysiology of AD and assisting in the early diagnosis and differentiation of the illness. The introduction of new medications requires molecular imaging techniques to precisely identify patients and evaluate their reaction to treatment. Molecular radiotracers are used to evaluate brain functions such as regional blood flow, glucose metabolism, and neurotransmitter deficits [10]. Advancements intechnology and radiopharmacology have allowed for the detection of aberrant protein deposition. This study aims to provide a summary of the current knowledge on radioligands used to visualize the pathophysiology and molecular mechanisms in AD by SPECT and PET imaging methods. The goal is to explore various approaches for evaluating SPECT and PET data and their significance in diagnosing AD. Technological and radio-pharmacological advancements in the past decade have made it possible to see abnormal protein deposits [11], while nuclear medicine imaging is actively expanding its focus to include Alzheimer's disease, to identify and study novel biochemical and molecular processes [12]. This systematic study evaluates the efficacy of contrast agents and molecular markers in diagnosing AD using PET and SPECT imaging techniques in animal models. [8, 9, 13-25]

2. Materials and Methods

A declaration on the PRISMA 2020 guidelines for systematic reviews and meta-analyses [26] was followed in the conduct of this systematic scoping review. In August 2023, PubMed was searched for papers written in English that were not limited by date. Based on the MeSH thesaurus and its entry terms, the keywords were selected. Alzheimer’s disease, dementia, and mice can be mentioned among the main keywords. To find more research, we also manually searched through all relevant reviews' reference lists. Duplicates were removed with the help of the Endnote (version 21.2.0.17387) and also manually based on the text review of the articles that were extracted from the same research project.

2.1.Selection and Exclusion Criteria

Screening of articles was done in two phases by three reviewers and any disagreements were discussed. Following a review of the article titles and abstracts in the first phase, the included papers moved on to the second step. In the second step, the full text of the articles was examined and finally, a number of related articles were included in the study. All animal studies about PET and SPECT imaging and AD were included as the primary goal. Reviews, non-original articles, and duplicates were not included.

2.2. Data Extraction

The purpose of data extraction was to determine the kind, ultimate usefulness or significance of contrast agents, and molecular indicators, as well as the disease type and the data quantity. Additionally, we retrieved the animal species and the Imaging device. All this information was first compiled in a table in a Word Document and then sorted and entered into an Excel Sheet (Microsoft Office LTSC Standard 2021).

2.3. Data Analysis

Data was analyzed using IBM Corp.'s SPSS 22 program (Endicott, NY, USA). The figures were created using Canva (version 2.259.1) and Excel (Microsoft Office LTSC Standard 2021) software for better clarity.

3. Results

Following PRISMA guidelines, we carried out a systematic scoping review of studies in which PET or SPECT imaging was used to track any cognitive impairment in animal models. As a result of the initial search, 172 original articles were included in the study. Finally, data from 116 studies were extracted (Figure 1).

Among the included articles, 30 studies (35.3%) have been conducted in the last five years. 110 studies (94.8%) worked on Alzheimer's, and the others worked on neurological diseases, including dementia.

We discovered that PET imaging was used in 100 studies (86.2%), SPECT imaging in 13 studies (12.9%), and both scans in 2 studies (1.7%), by looking at the usage percentage of each imaging device across investigations.

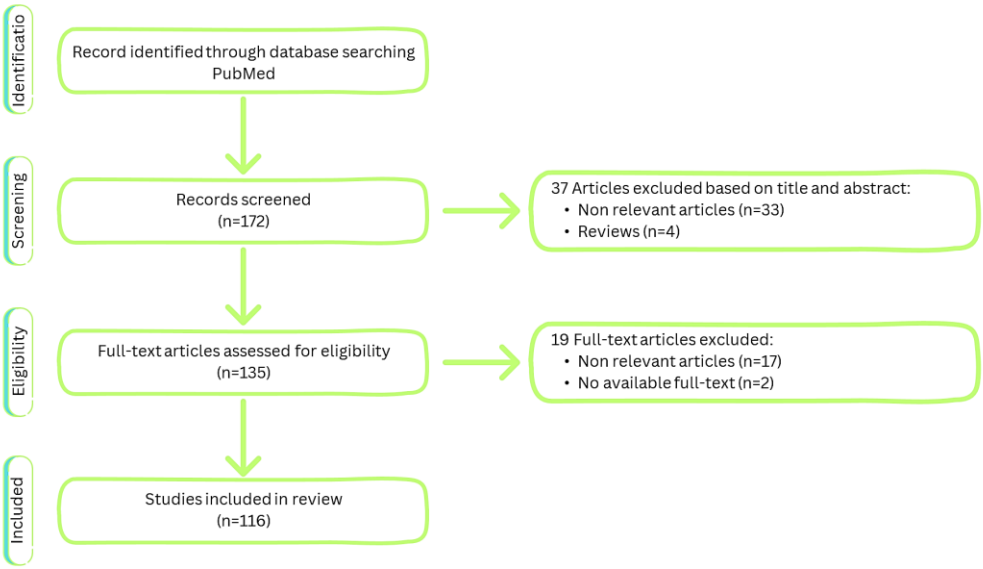

Figure 1. In accordance with the PRISMA principles, the flow diagram shown above illustrates the research selection method

The most often employed transgenic mouse strains in the studies were APP/PS1 (35 studies, 30.1%) and 5XFAD (11 studies, 9.5%). On average, 23 animals were used in each study.

You can see the results related to the amount of use of different types of contrast agents in Figure 2. 67 studies (57.8%) made use of [^{18}F] fluorodeoxyglucose and its derivatives as the contrast agent; 18 studies (15.5%) used [^{11}C] acetate; 10 studies (8.6%) used chemicals based on iodine; and 20 (17.2%) used other contrast agents. We also perused the percentage of Intended outcomes while using each contrast agent in studies, which is highlighted in different colors in Figure 2. 94% of the studies' utilization of [^{18}F] Fluorodeoxyglucose produced the intended outcomes among the contrast agents. Additionally, 94.4% of the usage of [^{11}C] Acetate and 90% of the use of Iodine-based chemicals resulted in the desired outcome, and 95% of the use of other contrast agents—which were employed less frequently—such as 99mTechnetium, Fluselenamyl, Copper (Cu) labeled benzofuran derivatives, etc.—also produced the desired outcomes. At last, 109 studies (94%) reached an intended outcomes.

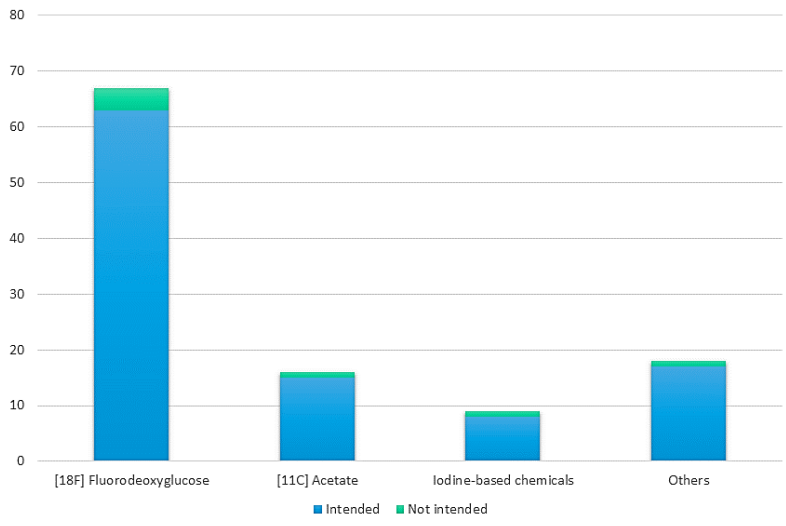

Figure 2. According to the above diagram, the contrast agents that were used in most studies were FDG, acetate, and iodine-based chemicals

The details related to the different traced Molecular indicators are shown in Figure 3. The most often used molecular indicators were Amyloid Beta (46.7%), Tau protein (10.7%), and Translocator protein (TSPO-6.6%). The next most common indicators were Acetylcholinesterase (AChE-4.9%), Growth hormone-releasing hormone (GRHR-1.6%), and Monoamine oxidase B (MAO-B -1.6%).

4. Discussion

The data interpretation aligns with prior research, underscoring the importance of imaging modalities in Alzheimer's Disease (AD) diagnosis. This highlights the need for further validation in clinical settings and assessment of contrast agent safety. PET and SPECT imaging shows promise for AD diagnosis when paired with appropriate contrast agents and molecular markers.

Previous studies, such as Valotassiou *et al.* [26] have established the potential of PET and SPECT imaging in early AD diagnosis and monitoring, emphasizing their role in detecting amyloid-beta plaques and tau protein tangles. These foundational studies paved the way for our current investigation into the clinical utility and safety of these imaging modalities. Future studies should prioritize expanding the use of PET and SPECT imaging in clinical practice to enhance early AD diagnosis and monitoring. Investigating the long-term safety and efficacy of contrast agents is crucial for confirming their clinical utility. This comprehensive analysis advances our understanding of the potential of imaging tools in AD diagnosis, warranting further exploration. Our findings on contrast agents and molecular indicators in AD diagnosis via PET and SPECT imaging raise critical questions about their clinical translation. It is essential to delve deeper into exploring practical applications in the clinical diagnosis and treatment of Alzheimer's disease.

Clinical Diagnosis: PET and SPECT imaging offers potential for early AD detection, providing insights into pathophysiology when combined with suitable contrast agents and molecular markers. These techniques aid in differentiating AD from other dementias and monitoring disease progression. Berti *et al.* [27] demonstrated that combined PET and SPECT imaging could improve diagnostic accuracy in early-stage AD patients.

Treatment Monitoring: Molecular indicators in PET and SPECT imaging play a crucial role in monitoring AD treatment efficacy. Tracking biomarker changes over time allows for therapeutic response assessment and personalized treatment adjustments. Pemberton *et al.* [28] showed that PET imaging could track changes in amyloid-beta levels in response to treatment, providing valuable feedback for therapeutic strategies.

Long-Term Safety and Efficacy: While further research on contrast agent safety is needed, translating these findings into clinical practice requires a comprehensive understanding of risks and benefits. Future studies should explore the long-term effects of contrast agents on patient outcomes to guide clinical decision-making.

Patient Stratification and Precision Medicine: Molecular imaging aids in identifying AD-specific

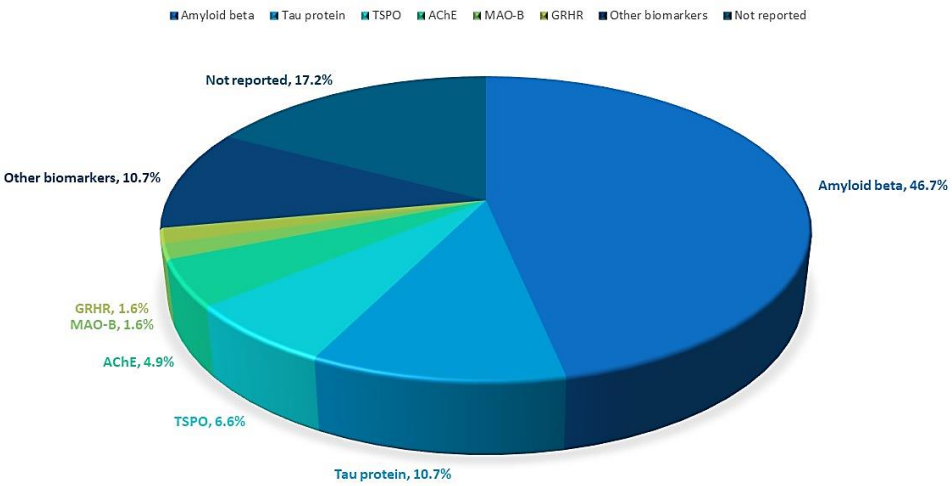

Figure 3. According to the above pie chart, the most molecular indicators that were tracked in the studies included amyloid beta, tau protein, and TSPO

biomarkers, facilitating patient stratification, and precision medicine. Tailoring treatment plans based on molecular profiles allows for targeted AD interventions, enhancing personalized care effectiveness. Arafah *et al.* [29] demonstrated that precision medicine guided by PET imaging biomarkers could significantly improve patient outcomes by customizing therapeutic interventions.

5. Conclusion

This study underscores the potential of PET and SPECT imaging as pivotal diagnostic tools for Alzheimer's Disease (AD) when utilized alongside appropriate contrast agents and molecular markers. However, a prudent acknowledgment of the study's limitations is imperative. The use of solely animal models raises the possibility that the results may not be seamlessly extrapolated to human subjects, necessitating further investigation into the efficacy of these contrast agents and molecular indicators in clinical settings. Moreover, the study's failure to assess the long-term consequences or safety of the employed contrast agents constitutes a notable limitation. To fortify and expand upon these findings, future research should prioritize the following key areas:

Clinical Trials: Rigorous clinical trials are essential to validate the efficacy and safety of the contrast agents and molecular markers delineated in this study. This rigorous validation procedure is pivotal in determining their applicability in human subjects and ensuring their reliability in clinical practice.

Long-Term Safety: A thorough exploration of the long-term effects and safety profiles of the contrast agents employed in PET and SPECT imaging is imperative. A comprehensive understanding of potential adverse effects and their implications for patient outcomes is paramount for informed clinical decision-making.

Biomarker Development: The pursuit of new and more specific molecular markers capable of enhancing the precision of AD diagnosis and monitoring is crucial. This encompasses the identification of biomarkers differentiating AD from other neurodegenerative conditions.

Personalized Medicine: An in-depth investigation into the integration of molecular imaging into personalized medicine approaches is essential. Tailoring treatment plans based on patients' molecular profiles empowers clinicians to target the underlying mechanisms of AD, thereby fostering more effective and personalized care.

Technological Advancements: The development of advanced imaging technologies enhancing the resolution and sensitivity of PET and SPECT imaging is a worthwhile investment. Improved early-stage AD detection and enhanced disease progression monitoring are poised to significantly impact the field. In conclusion, this research represents a substantive leap in our comprehension of AD diagnosis and lays the groundwork for further advancements in this domain. By addressing the delineated limitations and directing attention towards these specific research avenues, we can elevate the clinical utility of PET and SPECT imaging, thereby contributing significantly to the advancement of Alzheimer's treatment.

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