The perspectives of neurologists on positron emission tomography utility in multiple sclerosis: A qualitative study

Peer-reviewed author version

Ezzat, Daniel; Haest, Sion; Hertogs, Seger; Kalemkus, Eren; LEROI-WERELDS, Sara & HELLINGS, Niels (2024) The perspectives of neurologists on positron emission tomography utility in multiple sclerosis: A qualitative study. In: Multiple Sclerosis and Related Disorders, 92 (Art N° 106177).

DOI: 10.1016/j.msard.2024.106177
Handle: http://hdl.handle.net/1942/44784

Highlights

- Magnetic resonance imaging is used to visualize multiple sclerosis (MS).
- Positron emission tomography (PET) aids in capturing the full complexity of MS.
- Neurologists recognize the benefits of PET in both research and clinical settings.
- PET is valuable for understanding MS pathophysiology and developing new therapies.
- However, PET encounters several challenges before clinical integration is possible.

Abstract

Background

Magnetic resonance imaging (MRI) is the gold standard for imaging disease activity in multiple sclerosis (MS) patients. However, recent studies indicate that positron emission tomography (PET) may provide added value in visualizing MS disease in the future.

Objective

This study aims to investigate the barriers to implementing PET for MS patients and its potential added value in the context of MS.

Methods

11 semi-structured in-depth interviews with neurologists specialized in MS were conducted. The neurologists were selectively recruited from six medical centers in Belgium and the Netherlands. Inductive thematic analysis was used to analyze the data.

Results

The interviews revealed several hurdles that play a role in using PET for MS, including financial and scientific considerations. Potential clinical applications of PET were also identified, such as understanding unexplained symptoms, making a more accurate prognosis, evaluating the nature and seriousness of a lesion, and assessing disease activity. In addition, research applications were highlighted, including unraveling the pathophysiology of MS and developing new treatment options for MS.

Conclusion

Using PET is advancing our understanding of MS and can accelerate the development of novel therapies to combat its progression. However, its integration into routine clinical practice for MS remains a future prospect, contingent upon further technological advancements and supportive healthcare frameworks.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the myelin sheaths in the central nervous system. The characteristic brain and spinal cord lesions seen in MS are currently visualized using magnetic resonance imaging (MRI). Clinicians typically assess T2 hyperintense lesions and lesions exhibiting gadolinium enhancement. A T2 hyperintense lesion indicates tissue damage caused by inflammation and demyelination but is limited in clarifying specific disease processes (Thompson et al., 2018; Wattjes et al., 2021). Gadolinium contrast can be used to differentiate between active and inactive lesions. A gadolinium-enhancing lesion represents an area of blood-brain barrier (BBB) leakage and, thus, an active disease process. However, BBB disruption as depicted by gadolinium enhancement is less prominent or even absent in progressive forms of MS, making gadolinium contrast less reliable as a means to assess disease activity (Thompson et al., 2018; Wattjes et al., 2021).

The international McDonald criteria for diagnosing MS recommend performing at least one brain MRI scan in patients suspected of having MS (Thompson et al., 2018). While a detailed discussion of the McDonald criteria is beyond the scope of this article, it is important to realize that MRI has been deeply integrated into the diagnostic process of MS. In addition to its crucial role in the diagnosis, MRI is also essential for monitoring treatment progress and disease activity in MS (Wattjes et al., 2021). MRI has its limitations, as it can only measure changes in the physical properties of tissues, which are indirect results of pathological processes. Consequently, the ability of MRI to assess each component of the complex pathogenesis of MS is inherently constrained. In contrast, positron emission tomography (PET) enables the quantification of individual molecular disease processes through radioactive tracers (Bodini et al., 2021; Matthews, 2019).

Tracers targeting 18-kDa translocator protein (TSPO) are useful for visualizing neuroinflammation, with higher levels of TSPO being associated with a higher density of activated macrophages and microglia in MS (Bodini et al., 2021; Matthews, 2019; Nutma, et al., 2019). TSPO tracers that have been used in assessing MS include the first-generation tracer ^{11}C-PK11195, which is characterized by relatively high non-specific binding and a low signal-to-noise ratio (Bodini et al., 2021; Vonwinckel, et al., 1997; Banati et al., 2000). In contrast, several second-generation tracers, such as ^{11}C-PBR28 and ^{18}F-DPA714, offer lower non-specific binding and/or higher affinity for TSPO, enhancing their suitability for MS evaluation (Bodini et al., 2021; Datta, et al., 2017; Singhal, et al., 2018; Hagens et al., 2018; Bodini et al., 2020). The first key insight gained from applying TSPO PET in MS is that microglia and macrophage involvement in the disease's pathogenesis is fundamental from its onset, rather than being confined to the progressive stages (Banati et al., 2000; Giannetti et al., 2015; Rissanen et al., 2014; Politis et al., 2012). In addition, assessing innate immune cell activation using PET may serve as a predictor of clinical progression during follow-up (Sucksdorff et al., 2020). TSPO PET also provides a more precise understanding of immune cell localization and activity in both lesions and normal-appearing tissues, thereby improving the evaluation of inflammation beyond what MRI can detect (Bodini et al., 2021). For instance, prior research shows that a significant portion of white matter lesions considered active on PET scans with ^{18}F-DPA-714 were entirely invisible on gadolinium-contrast MRI scans (Bodini et al., 2020). Additionally, TSPO PET can evaluate the effectiveness of treatments in reducing microglial and macrophage activity in MS, as demonstrated in preliminary studies (Sucksdorff et al., 2017, 2019).

Current PET strategies to visualize astrocytes involve measuring ^{11}C-acetate, assessing monoamine oxidase B with ^{18}F-THK5351 and ^{11}C-deuterium-l-deprenyl, and evaluating the

adenosine A2A purinergic receptor using ^{11}C-TMSX (Kato et al., 2021; Takata et al., 2014; Ishibashi et al., 2020, 2021; Rissanen et al., 2013). However, astrocyte PET imaging is still in the early stages, and its potential to clarify the role of these glial cells in the pathogenesis of MS remains uncertain (Bodini et al., 2021).

Using PET with myelin-binding tracers provides a direct method for evaluating demyelination and remyelination. Several tracers can serve this purpose (Bodini et al., 2021; van der Weijden et al., 2023). ^{11}C-PiB is used as a tracer for Alzheimer's disease. Apart from its affinity for amyloid-β deposits, ^{11}C-PiB also binds to β-sheets of myelin basic protein (MBP), which enables its use in measuring in vivo myelin content changes within white matter lesions in patients with MS (Stankoff et al., 2011; Bodini et al., 2016). ^{11}C-MeDAS is a good example of a tracer with higher specificity to MBP, enabling more accurate measurement of myelin content (van der Weijden et al., 2022). Moreover, second-generation fluorinated tracers, such as ^{18}F-florbetaben and ^{18}F-florbetapir, show significant promise for myelin assessment (Matías-Guiu et al., 2015; Carotenuto et al., 2020). In fact, research on non-human primates indicates that ^{18}F-florbetaben and ^{18}F-florbetapir offer a higher signal-to-noise ratio in the white matter compared to ^{11}C-PiB or ^{11}C-MeDAS (Auvity et al., 2020).

Molecular imaging with PET can also contribute to assessing neuronal function (Bodini et al., 2021). The first tracer used for this purpose was ^{18}F-FDG, which indirectly measures neuronal function by quantifying glycolytic metabolism. In patients with MS, reduced ^{18}F-FDG uptake in the grey matter has been associated with fatigue and cognitive dysfunction, which suggests neuronal dysfunction and/or loss (Roelcke et al., 1997; Blinkenberg et al., 2000). Another tracer that assesses neuronal function is flumazenil (FMZ), an antagonist of the $GABA_A$ receptor in (sub)cortical grey matter. Using quantitative ^{11}C-FMZ PET showed diffuse neuronal damage in the grey matter of patients with MS (Freeman et al., 2015).

In sum, recent research indicates that several PET tracers offer added value in the context of MS. As PET imaging is currently not integrated in the decision-making process when monitoring MS patients in clinical practice, MRI remains the standard of care. This study aims to provide a neurologist's perspective on the barriers impeding the adoption of PET in clinical practice for MS patients as well as the potential added value of PET in the context of MS.

2. Methods

2.1. Study design

Qualitative research based on semi-structured in-depth interviews was used. This approach provides insights on why promising clinical tools have not yet been implemented in practice and highlights the potential added value these tools can bring (Hamilton and Finley, 2019). The Consolidated criteria for reporting qualitative research (COREQ) were used to prepare this manuscript (Tong et al., 2007).

2.2. Participant selection

Purposive sampling was used to align the sample with the research objectives, recognizing potential diversity in perspectives among distinct individuals (Campbell et al., 2020). Therefore, neurologists specialized in MS were selectively recruited, considering geographical distribution and variation in experience. Ultimately, 11 neurologists from six different medical centers in Belgium and the Netherlands were invited via email to partake in the study (Fig. 1).

Neurologist	Neurologist for over 7 years	Over 50% MS patients	MRI available in medical centre	PET available in medical centre	Familiarity with PET research	Country of medical practice
1	✓	×	✓	✓	+++	The Netherlands
2	×	✓	✓	✓	+	The Netherlands
3	✓	✓	×	×	+/-	Belgium
4	×	✓	✓	✓	+	Belgium
5	✓	✓	✓	✓	+	The Netherlands
6	✓	✓	✓	✓	++	The Netherlands
7	×	×	✓	✓	-	The Netherlands
8	✓	✓	✓	✓	+	Belgium
9	✓	✓	✓	×	++	Belgium
10	✓	✓	✓	×	+/-	Belgium
11	✓	✓	✓	×	+	Belgium

Fig. 1. Profiles of neurologists. Neurologists were numbered in the order in which they were interviewed. Neurologists 1, 2 and 3 were each from different medical centers. Neurologists 4 and 8 were from the same center, as were neurologist 5, 6 and 7, and neurologists 9, 10 and 11. A check mark indicates answering “Yes” and a cross indicates responding “No” to the statement in the upper dark orange box. Three pluses (+++) indicate a neurologist actively researching PET for MS. Two pluses (++) indicate a neurologist actively researching MRI for MS and capable of providing in-depth responses regarding PET. One plus (+) indicates a neurologist capable of providing in-depth responses regarding PET. A plus-minus (±) indicates a neurologist with limited knowledge of PET. A minus (-) indicates a neurologist unaware of PET research in the context of MS. PET, positron emission tomography; MRI, magnetic resonance imaging; MS, multiple sclerosis.

2.3. Data collection

Data was collected through semi-structured in-depth interviews, with each neurologist being individually interviewed by two researchers (DE, SH, SH, EK), using a pre-established interview guide (Fig. 2). Each interview was audio-recorded and ranged from a minimum of 16 min to a maximum of 50 min, with an average duration of 33 min. Subsequently, each recording was transcribed verbatim into an anonymized format to analyze the data. Each transcription was manually drafted by one researcher and proofread by at least one other researcher.

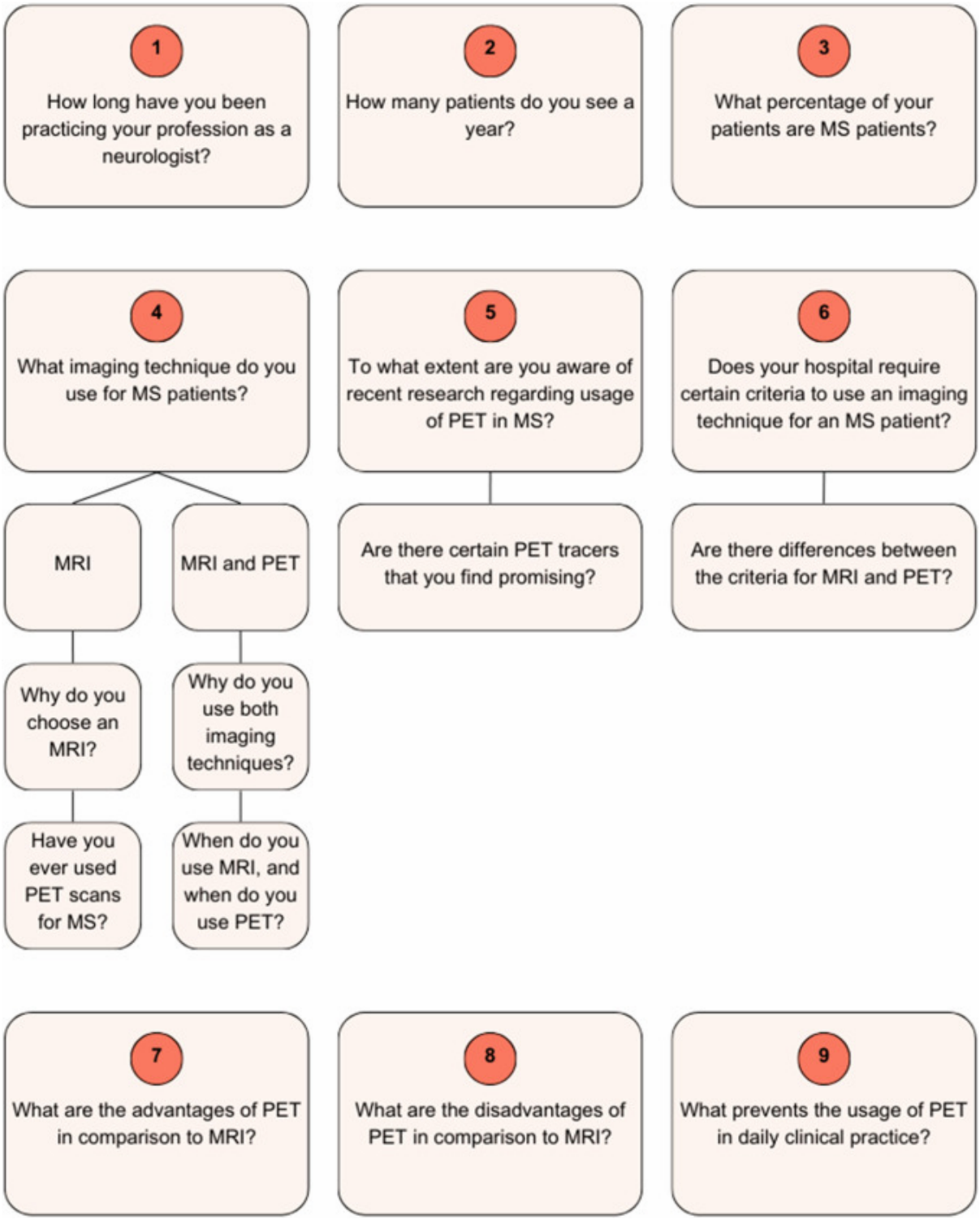

Fig. 2. Interview guide. PET, positron emission tomography; MRI, magnetic resonance imaging; MS, multiple sclerosis.

2.4. Data analysis

The same researchers (DE, SH, SH, EK) conducted an inductive thematic analysis to process the data into workable themes and draw emerging conclusions (Castleberry and Nolen, 2018). During data analysis, relevant statements made by the neurologists were assigned specific codes. To promote the objectivity of the data analysis, each transcript was independently analyzed by at least two researchers. The coding sheets from two or more

researchers were compared and merged into a single coding sheet. Regular discussions were held to reach a consensus on the interpretation of the data. The outcome of this process was a list of quotes with corresponding codes. Using this list, key themes were identified (Busetto et al., 2020).

To determine the necessary number of semi-structured interviews to address this study's research questions, data saturation was assessed. This is the point at which no significant new information is obtained from conducting additional interviews (Busetto et al., 2020).

2.5. Ethical considerations

This study was approved by the Committee for Medical Ethics of Hasselt University (CME2023/001).

All neurologists agreed to participate in semi-structured interviews and signed written informed consent. The neurologists had the right to withdraw from the interview at any time.

3. Results

In total, 62 codes were used. Neurologists 1, 2, and 3 collectively accounted for 48 of the 62 codes. Neurologists 4 and 5 introduced seven new codes, while neurologists 6, 7, and 8 each contributed two new codes. No additional codes were introduced thereafter, except for one final new code by neurologist 11. These findings indicated data saturation (Busetto et al., 2020).

3.1. Availability and logistics

The first theme that emerged from the data was availability and logistics. Participants indicated that the number of available PET scanners is more limited compared to MRI scanners.

"I was trained in a hospital with only one PET scanner. So, if I were to line up all my MS patients to undergo a PET scan, there would have been a very long line at the door. I think the capacity to conduct PET scans could be improved."

• Neurologist 2

Besides, a limited variety of PET tracers is available for MS, and only a few companies or centers produce them. Moreover, once the PET tracers have been acquired, they must be stored safely and used within a time-sensitive window due to their radioactivity and half-life (Crișan et al., 2022).

"The PET scanner already costs a few million. You also need a device to store the radioactive materials properly. Then there's the cost of the ligands, which usually come from a central factory. So, there is a significant hurdle for non-academic hospitals to start using a PET scanner."

• Neurologist 1

In addition, neurologists can independently interpret MRI scans because they have been deeply integrated into clinical practice. Proficient PET interpretation, however, would likely require additional training for many neurologists.

"For me, the significant advantage is that I can personally evaluate an MRI scan. I have limited experience with PET scans. When it comes to a PET scan, I am truly dependent on a nuclear physician for the results."

• Neurologist 7

3.2. Cost

The costs associated with using PET are exceedingly high, as mentioned by many neurologists. In particular, hospitals must consider the expensive radioactive tracers. Compared to contrast agents used in MRI, PET tracers involve significantly higher costs. This makes a reimbursing authority less inclined to cover PET scan reimbursement for MS.

"If something is very expensive or not readily available, then there is an issue with reimbursement, and it becomes more difficult to use. This hinders its rapid and straightforward applicability. Consequently, it may result in selection of specific patients."

• Neurologist 11

To justify the high costs associated with PET scans, neurologists emphasized that there must be clinical relevance in performing a PET scan. There should be clear and substantial added value compared to the conventional MRI scan.

"You have to question what the added value of PET is compared to MRI. This has to be thoroughly and unequivocally demonstrated if you want to carve out a place for PET in the landscape of MS patients."

• Neurologist 8

3.3. Scientific considerations

Neurologists highlighted the need for more scientific research. First of all, the resolution of PET significantly lags behind MRI, making it difficult to detect smaller lesions or changes. Therefore, efforts should be made to improve the resolution of PET. However, there is a fundamental limit to the spatial resolution achievable with PET, which can never approach MRI's spatial resolution.

"PET scans provide more global images, with much less detail; the voxels are much larger, and the slices are coarser. MS is a condition that needs to be seen at a detailed level. Therefore, I think the added value of a PET scan could be there, but not for inflammation. For that, the MRI scan is much more accurate."

• Neurologist 6

Additionally, more tracers must be developed to bind to valuable targets within the context of MS, such as T-cells and B-cells.

"Suppose we have tracers for, let's say, T-cells. Then we could say: “In this patient, you have T-cell activity in almost all lesions, so I should administer something that specifically targets T-cells.” But those tracers still need to be developed. There are a few, but it's all in very specialized centers."

• Neurologist 9

Lastly, the degree to which a PET tracer is specific for its target is also important. When a PET tracer is not specific enough to visualize a particular MS disease process, it will also bind elsewhere. This results in false-positive information, complicating the interpretation of a PET scan.

"All the ligands we use now are not specific enough. Even those used for Alzheimer's are actually quite non-specific. They may bind to amyloid, but some of them mainly bind to any

β-pleated sheet. While it is abundant in amyloid, it is also found in other places. So, these ligands need to be much more specific."

• Neurologist 1

3.4. Safety

MRI operates based on electromagnetic principles and is not harmful to patients' cells. The same cannot be said for the radioactivity associated with PET scans.

"When you talk about nuclear scans, you also deal with safety and such. So, that will limit it a bit. It will be something that maybe cannot be done so frequently."

• Neurologist 11

There are also specific patient groups to consider, especially for MRI. For example, several neurologists mentioned claustrophobic patients. While both MRI and PET scanners involve patients lying in tunnels, PET scans tend to be more tolerable for individuals with claustrophobia.

"MRI has the disadvantage that you have to lie in a narrow space for a long time, which is not equally suitable for all patients. PET, on the other hand, offers a bit more space, making it more comfortable for some patients."

• Neurologist 6

MRI scans are also contraindicated in patients with metal objects in their body, such as old pacemakers or certain sacral neurostimulators.

"We have a lot of MS patients with a sacral neurostimulator because they have bladder problems due to their MS. There can be issues with MRI compatibility in such cases."

• Neurologist 4

3.5. Potential added value of PET

A significant limitation of MRI is the lack of quantitative information. Although MRI provides valuable data regarding the presence and location of lesions, it does not grant molecular or functional information about MS. PET offers greater insights into the nature and severity of MS lesions, potentially opening the door to new treatment strategies based on precise lesion processes. Moreover, PET could determine disease activity in progressive forms of MS, whereas MRI with gadolinium contrast showed limited reliability in this regard.

"You could effectively examine the tissue's metabolic activity. Depending on the tracers, you could, for example, say: “We see a high level of activated microglia here, indicating that this lesion is likely growing significantly at the moment.” This is something you can never do with an MRI because all you see on an MRI is a white spot. You don't see what's happening inside that white spot."

• Neurologist 9

The ability of PET to reveal disease activity in brain regions seemingly unchanged on MRI can also contribute to understanding symptoms not accounted for by MRI.

"The progressive phase is usually not accompanied by MRI changes. So, you perform a scan and tell the patient: “Your MRI scan is stable.” Meanwhile, the patient is clinically deteriorating."

• Neurologist 5

Furthermore, a few neurologists mentioned that some patients may struggle with this themselves.

"Patients really want to know if there is any change. If nothing has changed, and they still feel like they are getting worse, it's as if their perception is not believed."

• Neurologist 3

Some neurologists also suggested that PET could aid in prognosis. Using PET, clinicians could potentially predict which patients are at high risk of developing progressive MS.

"In terms of prognosis, PET might be meaningful. For example, I would like to know whether my patient has a strong capacity for myelin repair or not at all. If you know your patient recovers well, then you are less inclined to escalate treatment quickly. Whereas if you already know from the beginning that this is someone with very little reserves, you are likely to treat them more aggressively."

• Neurologist 4

PET can be a valuable tool for researching disease processes during the progressive phase of MS. Therefore, a few neurologists mentioned that PET is already highly intriguing for unraveling the pathophysiology of MS.

"For research purposes, using PET scans in secondary progressive MS and observing what happens there, that seems very interesting to me."

• Neurologist 5

Furthermore, most neurologists indicated that PET could contribute to the development of new treatments. For instance, PET could assess the degree of remyelination for potential medications that promote this process.

"PET can also be applicable in research to ensure the development of new drugs. I think it can provide very interesting insights in drug development."

• Neurologist 8

4. Discussion

The interviewed neurologists displayed a range of familiarity with PET in the context of MS (Fig. 1). Eight neurologists demonstrated sufficient understanding to provide in-depth responses. Notably, neurologist 1 is actively researching PET applications in MS, while neurologists 6 and 9 are involved in MRI research for MS. Neurologists 3 and 10 had limited knowledge of PET, and neurologist 7 was unaware of PET research within the context of MS. This variation in expertise contributed to a well-rounded analysis, as those with a deeper understanding tended to provide more specific insights into potential benefits and limitations, whereas those less familiar emphasized important points around accessibility and integration into clinical workflows.

The findings of this study highlight that even the current gold standard, MRI, has its limitations. Although PET has the potential to provide valuable information in MS, there are currently several bottlenecks hindering its use in clinical practice. This study highlights many common implementation barriers, as described by the most recent Consolidated Framework for Implementation Research (CFIR) (Damschroder et al., 2022). First, new and more specific PET tracers for MS should be developed, and efforts should be made to enhance

the resolution of PET. When considering the accessibility of PET scanners, enhancing the widespread availability through support from national healthcare systems could be advantageous. However, one can also argue that it is beneficial to send patients to specific centers. This would mirror standard practice for other expensive techniques, such as proton therapy, and would have the significant advantage of centralizing expertise. Second, additional studies are needed to demonstrate the added value of PET tracers in progressive MS. This could potentially be accomplished through a comparative analysis involving PET tracers in contrast to MRI. Third, reimbursement for PET scans has to be established for appropriate indications within the context of MS in order to facilitate its effective integration into clinical practice. However, justifying reimbursements is likely to depend on the scientific evidence provided to demonstrate the added value of PET.

This qualitative study is best understood within the confinements of its limitations. First of all, our study is based on the opinions of neurologists and does not include input from other healthcare providers. The perspectives of nuclear medicine physicians, for instance, could be very insightful. The decision to interview neurologists specialized in MS was primarily driven by their frequent contact with MS patients. They are the ones who discuss MS care with patients and determine when imaging is necessary. Furthermore, the opinions of MS patients themselves were not surveyed. However, by interviewing neurologists specialized in MS, at least some aspects of the patients' perspectives were indirectly captured. Additionally, this study was conducted with neurologists from two West-European countries. Consequently, the perspectives of neurologists in nations with less developed healthcare systems were not taken into account. It also has to be emphasized that there were 11 neurologists from six different medical centers, which means that for a few centers more than one neurologist was interviewed. While there is a possibility of mutual influence among neurologists from the same centers, this seems unlikely given that the interviews were conducted separately for each neurologist and there was notable variation in their knowledge (Fig. 1). To this point, it is worth noting that the first five neurologists represented different centers and contributed significantly to our analysis, accounting for 55 out of 62 codes (88.7 %). This suggests that any bias towards specific centers has been minimized.

5. Conclusion

In conclusion, PET represents an innovative approach that is increasingly valuable in the context of MS. Using PET is advancing our understanding of this complex disease and can accelerate the development of novel therapies to combat its progression. However, its integration into routine clinical practice for MS remains a future prospect, relying on further technological advancements and a robust framework within healthcare systems.

CRediT authorship contribution statement

Daniel Ezzat: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis. **Sion Haest:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Seger Hertogs:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Eren Kalemkus:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Sara Leroi-Werelds:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Niels Hellings:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors have no relevant financial or non-financial conflicts of interest to disclose.

Acknowledgments

The authors would like to express their gratitude to all the neurologists who shared their perspectives for this study. Special thanks are also due to Jochen Bergs for critically reviewing the manuscript.

References

1. Auvity et al., 2020 S. Auvity, M. Tonietto, F. Caillé, *et al.*

   Repurposing radiotracers for myelin imaging: a study comparing 18F-florbetaben, 18F-florbetapir, 18F-flutemetamol,11C-MeDAS, and 11C-PiB

   Eur. J. Nucl. Med. Mol. ImAging, 47 (2) (2020), pp. 490-501

2. Banati et al., 2000 R.B. Banati, J. Newcombe, R.N. Gunn, *et al.*

   The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity

   Brain, 123 (11) (2000), pp. 2321-2337

3. Blinkenberg et al., 2000 M. Blinkenberg, K. Rune, C.V. Jensen, *et al.*

   Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS

   Neurology., 54 (3) (2000), pp. 558-564

4. Bodini et al., 2016 B. Bodini, M. Veronese, D. García-Lorenzo, *et al.*

   Dynamic Imaging of Individual Remyelination Profiles in Multiple Sclerosis

   Ann. Neurol., 79 (5) (2016), pp. 726-738

5. Bodini et al., 2020 B. Bodini, E. Poirion, M. Tonietto, *et al.*

   Individual mapping of innate immune cell activation is a candidate marker of patient-specific trajectories of worsening disability in multiple sclerosis

   J. Nucl. Med., 61 (7) (2020), pp. 1043-1049

6. Bodini et al., 2021 B. Bodini, M. Tonietto, L. Airas, *et al.*

   Positron emission tomography in multiple sclerosis - straight to the target

   Nat. Rev. Neurol., 17 (11) (2021), pp. 663-675

7. Busetto et al., 2020 L. Busetto, W. Wick, C. Gumbinger

   How to use and assess qualitative research methods

   Neurol. Res. Pract., 2 (2020), p. 14

8. Campbell et al., 2020 S. Campbell, M. Greenwood, S. Prior, *et al.*

   Purposive sampling: complex or simple? Research case examples

   J. Res. Nurs., 25 (8) (2020), pp. 652-661

9. Carotenuto et al., 2020 A. Carotenuto, B. Giordano, G. Dervenoulas, *et al.*

   [^{18}F]Florbetapir PET/MR imaging to assess demyelination in multiple sclerosis

Eur. J. Nucl. Med. Mol. ImAging, 47 (2) (2020), pp. 366-378

10. Castleberry and Nolen, 2018 A. Castleberry, A. Nolen

    Thematic analysis of qualitative research data: is it as easy as it sounds?

    Curr. Pharm. Teach. Learn., 10 (6) (2018), pp. 807-815

11. Crișan et al., 2022 G. Crișan, N.S. Moldovean-Cioroianu, D.G. Timaru, *et al.*

    Radiopharmaceuticals for PET and SPECT imaging: a literature review over the last decade

    Int. J. Mol. Sci., 23 (9) (2022), p. 5023

12. Damschroder et al., 2022 L.J. Damschroder, C.M. Reardon, M.A.O. Widerquist, *et al.*

    The updated Consolidated Framework for Implementation Research based on user feedback

    Implement. Sci., 17 (1) (2022), p. 75

13. Datta et al., 2017 G. Datta, A. Colasanti, N. Kalk, *et al.*

    ^{11}C-PBR28 and ^{18}F-PBR111 detect white matter inflammatory heterogeneity in multiple sclerosis

    J. Nucl. Med., 58 (9) (2017), pp. 1477-1482

14. Freeman et al., 2015 L. Freeman, D. Garcia-Lorenzo, L. Bottin, *et al.*

    The neuronal component of gray matter damage in multiple sclerosis: a [(11) C]flumazenil positron emission tomography study

    Ann. Neurol., 78 (4) (2015), pp. 554-567

15. Giannetti et al., 2015 P. Giannetti, M. Politis, P. Su, *et al.*

    Increased PK11195-PET binding in normal-appearing white matter in clinically isolated syndrome

    Brain, 138 (1) (2015), pp. 110-119

16. Hagens et al., 2018 M.H.J. Hagens, S.V. Golla, M.T. Wijburg, *et al.*

    In vivo assessment of neuroinflammation in progressive multiple sclerosis: a proof of concept study with [^{18}F]DPA714 PET

    J. Neuroinflammation., 15 (1) (2018), p. 314

17. Hamilton and Finley, 2019 A.B. Hamilton, E. Finley

    Qualitative methods in implementation research: an introduction

    Psychiatry Res., 280 (2019), Article 112516

18. Ishibashi et al., 2020 K. Ishibashi, Y. Miura, K. Hirata, *et al.*

    18F-THK5351 PET Can Identify Astrogliosis in Multiple Sclerosis Plaques

    Clin. Nucl. Med., 45 (2) (2020), pp. e98-e100

19. Ishibashi et al., 2021 K. Ishibashi, M. Kameyama, Y. Miura, *et al.*

Head-to-head comparison of the two MAO-B radioligands, 18F-THK5351 and 11C-L -deprenyl, to visualize astrogliosis in patients with neurological disorders

Clin. Nucl. Med., 46 (1) (2021), pp. e31-e33

20. Kato et al., 2021 H. Kato, T. Okuno, K. Isohashi, *et al.*

Astrocyte metabolism in multiple sclerosis investigated by 1-C-11 acetate PET

J. Cereb. Blood Flow Metab., 41 (2) (2021), pp. 369-379

21. Matías-Guiu et al., 2015 J.A. Matías-Guiu, M.N. Cabrera-Martín, J. Matías-Guiu, *et al.*

Amyloid PET imaging in multiple sclerosis: an (18)F-florbetaben study

BMC. Neurol., 15 (2015), p. 243

22. Matthews, 2019 P.M. Matthews

Chronic inflammation in multiple sclerosis – seeing what was always there

Nat. Rev. Neurol., 15 (10) (2019), pp. 582-593

23. Nutma et al., 2019 E. Nutma, J.A. Stephenson, R.P. Gorter, *et al.*

A quantitative neuropathological assessment of translocator protein expression in multiple sclerosis

Brain, 142 (11) (2019), pp. 3440-3455

24. Politis et al., 2012 M. Politis, P. Giannetti, P. Su, *et al.*

Increased PK11195 PET binding in the cortex of patients with MS correlates with disability

Neurology., 79 (6) (2012), pp. 523-530

25. Rissanen et al., 2013 E. Rissanen, J.R. Virta, T. Paavilainen, *et al.*

Adenosine A2A receptors in secondary progressive multiple sclerosis: a [(11)C]TMSX brain PET study

J. Cereb. Blood Flow Metab., 33 (9) (2013), pp. 1394-1401

26. Rissanen et al., 2014 E. Rissanen, J. Tuisku, J. Rokka, *et al.*

In vivo detection of diffuse inflammation in secondary progressive multiple sclerosis using PET imaging and the radioligand ^{11}C-PK11195

J. Nucl. Med., 55 (6) (2014), pp. 939-944

27. Roelcke et al., 1997 U. Roelcke, L. Kappos, J. Lechner-Scott, *et al.*

Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study

Neurology., 48 (6) (1997), pp. 1566-1571

28. Singhal et al., 2018 T. Singhal, K. O'Connor, S. Dubey, *et al.*

18F-PBR06 versus 11C-PBR28 PET for assessing white matter translocator protein binding in multiple sclerosis

Clin. Nucl. Med., 43 (9) (2018), pp. e289-e295

29. Stankoff et al., 2011 B. Stankoff, L. Freeman, M. Aigrot, *et al.*

Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-^{11}C]-2-(4′-methylaminophenyl)- 6-hydroxybenzothiazole

Ann. Neurol., 69 (4) (2011), pp. 673-680

30. Sucksdorff et al., 2017 M. Sucksdorff, E. Rissanen, J. Tuisku, *et al.*

Evaluation of the effect of fingolimod treatment on microglial activation using serial PET imaging in multiple sclerosis

J. Nucl. Med., 58 (10) (2017), pp. 1646-1651

31. Sucksdorff et al., 2019 M. Sucksdorff, J. Tuisku, M. Matilainen, *et al.*

Natalizumab treatment reduces microglial activation in the white matter of the MS brain

Neurol. Neuroimmunol. Neuroinflamm., 6 (4) (2019), p. e574

32. Sucksdorff et al., 2020 M. Sucksdorff, M. Matilainen, J. Tuisku, *et al.*

Brain TSPO-PET predicts later disease progression independent of relapses in multiple sclerosis

Brain, 143 (11) (2020), pp. 3318-3330

33. Takata et al., 2014 K. Takata, H. Kato, E. Shimosegawa, *et al.*

11C-acetate PET imaging in patients with multiple sclerosis

PLoS. One, 9 (11) (2014), Article e111598

34. Thompson et al., 2018 A.J. Thompson, B. Banwell, F. Barkhof, *et al.*

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Lancet Neurol., 17 (2) (2018), pp. 162-173

35. Tong et al., 2007 A. Tong, P. Sainsbury, J. Craig

Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups

Int. J. Qual. Health Care, 19 (6) (2007), pp. 349-357

36. van der Weijden et al., 2022 C. van der Weijden, J. Meilof, A. van der Hoorn, *et al.*

Quantitative assessment of myelin density using [^{11}C]MeDAS PET in patients with multiple sclerosis: a first-in-human study

Eur. J. Nucl. Med. Mol. ImAging, 49 (10) (2022), pp. 3492-3507

37. van der Weijden et al., 2023 C. van der Weijden, E. Biondetti, I.W. Gutmann, *et al.*

Quantative myelin imaging with MRI and PET: an overview of techniques and their validation status

Brain, 146 (4) (2023), pp. 1243-1266

38. Vonwinckel et al., 1997 E. Vonwinckel, D. Reutens, B. Becher, *et al.*

PK11195 binding to the peripheral benzodiazepine receptor as a marker of microglia activation in multiple sclerosis and experimental autoimmune encephalomyelitis

J. Neurosci. Res., 50 (2) (1997), pp. 345-353

39. Wattjes et al., 2021 M.P. Wattjes, O. Ciccarelli, D.S. Reich, *et al.*

2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis

Lancet Neurol., 20 (8) (2021), pp. 653-670

[#] Equally contributing senior authors.