Clinical and Translational Imaging (2023) 11:315–319
https://doi.org/10.1007/s40336-023-00572-6

SPOTLIGHT

Neuroimaging with PET/MR: moving beyond 3 T in preclinical systems, when for clinical practice?

Arosh S. Perera Molligoda Arachchige[1]

Received: 28 February 2023 / Accepted: 11 May 2023 / Published online: 30 May 2023

With the advent of ultra-high-field (UHF) imaging and integrated PET/MRI systems at the beginning of the twenty-first century, it seems that the field of neurological disease research has unlocked the potential to reach new heights, since this new technology gives access to a world of intriguing possibilities including tools to analyze complex neuronal mechanisms and improves our understanding of neurological disease processes. This is because MRI which has great spatial and temporal resolution and PET, being the gold standard for molecular imaging due to its high specificity depending on which tracer is used makes it possible for these integrated ultra-high-field MR-PET systems to yield superb resolution along with highly specific molecular data [1, 2]. To put it more simply, neurotransmission is driven by either receptors or neurotransmitters or modulated by drugs which is the domain of PET, while MRI on the contrary acts at a systemic level allowing localization and fMRI-aided analysis of complex neural mechanisms [3].

Integrated PET/MRI, as compared with acquisitions on two separate systems with post hoc fusion, provides several unique advantages. Regardless of the field strength, one of the fundamental benefits of integrated PET/MR is that synchronous image acquisition being a one-stop-shop procedure has made it easier to recruit volunteers for imaging studies during experimental studies due to increased patient comfort and could be especially helpful in subjects with reduced ability to cooperate such as those with dementia [1]. Moreover, it improves overall efficiency when considering cases that have to undergo both imaging procedures. The overall acquisition time can be invested in multiple contrast weightings, spectroscopic information, and also in adding dynamic information in PET and/ or MR [4]. In performing an integrated PET/MR of the brain, the benefits are even more marked. First, there exist relatively few sources of involuntary cranial motion such as pulsation or tremor (for example, in Parkinson's disease). As a result, if patients cooperate, sequential scanning and post hoc fusion may be possible. However, it should be highlighted that, to overcome this issue, motion correction algorithms have been developed to further improve image quality when imaging uncooperative patients or individuals with tremor [4]. This is because, when PET and MRI are used in tandem, it is possible to monitor patient motion with fast MRI sequences and utilize this information to cancel out motion in the concurrently obtained PET pictures [5]. Nevertheless, fully integrated PET/MRI is only required for the simultaneous imaging of temporally related processes, such as the regional consumption of glucose and oxygen in functional PET/MRI studies [5]. Second, the excellent symmetry and extremely low deformability of the head make it easier to use software-based approaches for post hoc rigid motion correction and co-registration. When integrated whole-body devices were not yet available, the head's comparable modest size allowed for combined PET/MRI using PET inserts in standard MR scanners. Additionally, due to the geometry of the head, homogenous magnetic fields are possible during ultra-high-field MRI, which can produce excellent MR data that can be fused with PET [5].

Such PET/MRI technology has been efficiently utilized even in translational imaging studies mainly using scanners at lower field strengths in the context of stroke, tumors, and several neurological disorders/neurological conditions, such as Parkinsonian syndromes, epilepsy, Alzheimer's disease, etc. Previous reviews have discussed neuroimaging applications of PET/MR at conventional field strengths as it has been already documented by several reviews, including Son et al. [6] and Miller-Thomas et al. [7].

Although the notion of a hybrid PET/MRI was developed before that for PET/CT, it took longer to come to fruition because of technical challenges, the complexity of integrating PET within an intense magnetic field, and the

✉ Arosh S. Perera Molligoda Arachchige
aroshshavinda.pereramolligodaarachchige@st.hunimed.eu

[1] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, 20072 Pieve Emanuele, MI, Italy

greater cost. The majority of preclinical MRI equipment manufacturers now favor PET insert designs as a solution to the cost problem and to make use of already installed MRI systems. Due to the high static magnetic field, the gradient coils' quick switching, and the interaction of the radiofrequency (RF) field with the PET electronics, the design of a PET insert for preclinical imaging needed to address several technical issues. The gradients in preclinical MRI are stronger than those in clinical systems, which increases the likelihood of undesirable interactions. The initial designs for PET detectors that may be used with MRIs relied on ordinary photomultiplier tubes that were positioned outside of the magnetic field and read out using lengthy optical fibers. Due to the restricted interior space in the MRI, the intense magnetic fields (7–9.4 T) utilized in preclinical scanners, and the declining PET performance (energy and time resolution), this strategy is no longer being investigated [8]. These restrictions have now been removed thanks to solid-state detectors like silicon photomultipliers (SiPM), and more recently, avalanche photodiodes (APD). These detectors perform well even when placed inside magnet bores that resemble photomultiplier tubes, because they are insensitive to strong magnetic fields [8, 9]

So how does specifically the integration of ultra-high-field imaging benefit? A study by Hammer et al. [10] showed that magnetic-field strengths above 5 T can further improve PET image quality by reducing the mean free positron path between annihilation and emission. Furthermore, the improvement in contrast with the increase in field strength does not increase linearly but exponentially. Thus, the images acquired with the 9.4 T MRI offer greatly improved spatial resolution, about 2.5 times that given by the 1.5 T MRI as well as higher functional (BOLD) contrast [11].

While no commercially integrated human MR-PET scanner with a high-field MR magnet (> 3 T) is yet available, integrated small-animal MR-PET operating at field strengths of 4.7 T, 7 T, and 9.4 T have been developed and are now commercially available. Indeed, the 9.4 T PET/MRI, the very latest innovation in preclinical imaging of animal models is a PET system coupled with a cryogen-free 9.4 T MR that enables simultaneous MR and PET imaging data acquisition. To our knowledge, the ultra-high-field PET/MRIs are currently manufactured exclusively by "MR Solutions (UK) and Bruker BioSpin Corp. (which manufactures PET inserts for high field MR; see Fig. 1) and are already available in a few academic centers worldwide [12, 13].

As of 12 October 2017, the Food and Drug Administration (USA) approved 7.0 T whole-body MRI for clinical use. Images obtained from 7.0 T MRI showed markedly improved images with a high signal-to-noise ratio. This improvement has enabled the visualization of many structures which would be hardly visible in lower magnetic-field systems in particular in areas that require high spatial resolution, such as the hippocampus, thalamus, and brainstem which have complicated substructures as well as super-fine structures including neuronal bundles in the pons, fine blood vessels (such as lenticulostriate arteries) without invasive contrast agents, and in vivo and substantia nigra with excellent image

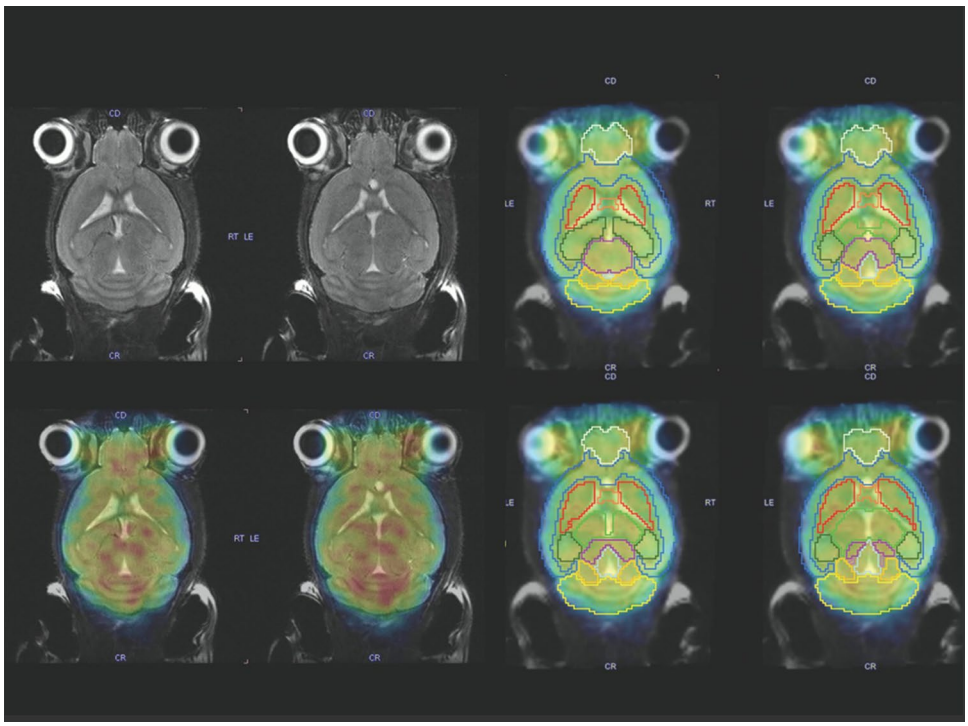

Fig. 1 High-resolution mouse brain imaging using 18F-FDG-PET/MR at 9.4 T and registration to PMOD brain atlases. Image courtesy: Department of Radiology and Imaging Sciences Indiana University

contrast (see Fig. 2). Therefore, combined ultra-high-field PET/MR would be most useful to assess neuropsychiatric disorders involving these regions [1].

These integrated ultra-high-field PET/MR systems could be useful for early non-invasive diagnosis of brain tumors through in vivo imaging. A study by Viel et al. which investigated tracers for angiogenic and infiltrative glioblastoma using 7 T MRI and PET performed separately showed that 11C-methionine accumulation was more specific than 18-fluorothymidine for the detection of angiogenic glioblastoma [14]. Indeed, amino acid PET tracers are now the most used and best-studied PET tracers for brain tumor diagnosis. For the diagnosis of glioblastoma (GBM), Lohmann et al. have reviewed the use of amino acid PET in conjunction with MR spectroscopy (MRS), perfusion- and diffusion-weighted imaging (PWI, DWI), and chemical exchange saturation transfer (CEST) [14, 15]. This approach becomes even more intriguing now that ultra-high-field MRI scanners with magnetic-field strengths of 7 T or higher are commonly accessible and enable high-resolution comparative anatomical and metabolic MR imaging. This is because ADC maps and certain PWI techniques, in particular, arterial spin labeling (ASL) are thought to benefit from higher field strengths [15]. When using ASL, a particular radiofrequency pulse is used to magnetically mark endogenous water molecules in blood vessels. When these labeled molecules pass through the target tissue, the signal strength decreases proportionately to the perfusion. The signal-to-noise ratio of ASL is, however, fundamentally low from having no contrast agent, necessitating repetitive signal averaging, which lengthens acquisition durations. Higher magnetic-field strengths have a considerable positive impact on ASL. Hybrid ultra-high-field PET/MRI scanners could therefore increase their clinical utility in the future [15].

Furthermore, single-labeled cells have been demonstrated to be detectable in vivo in rats using UHF MR imaging (due to the higher attainable spatial resolution) in conjunction with specialized contrast agents, such as micro- and nanoparticles. This skill can be used in many different contexts, including the assessment of cell function or metabolism via PET. It is interesting to note that dual-mode functionalized PET/MR nanoprobes have been produced, and they can theoretically be used to spatially track the nanoparticle (by MR), while the radiolabeled payload would enable quantification of the uptaken/interacting biomarker. Thus, the next breakthrough in brain tumor treatment might involve drug delivery and intelligent probes [16].

In addition, UHF PET/MRI could aid the validation of imaging protocols as it has been demonstrated in the study by Bos et al. comparing arterial spin labeling at 7 T

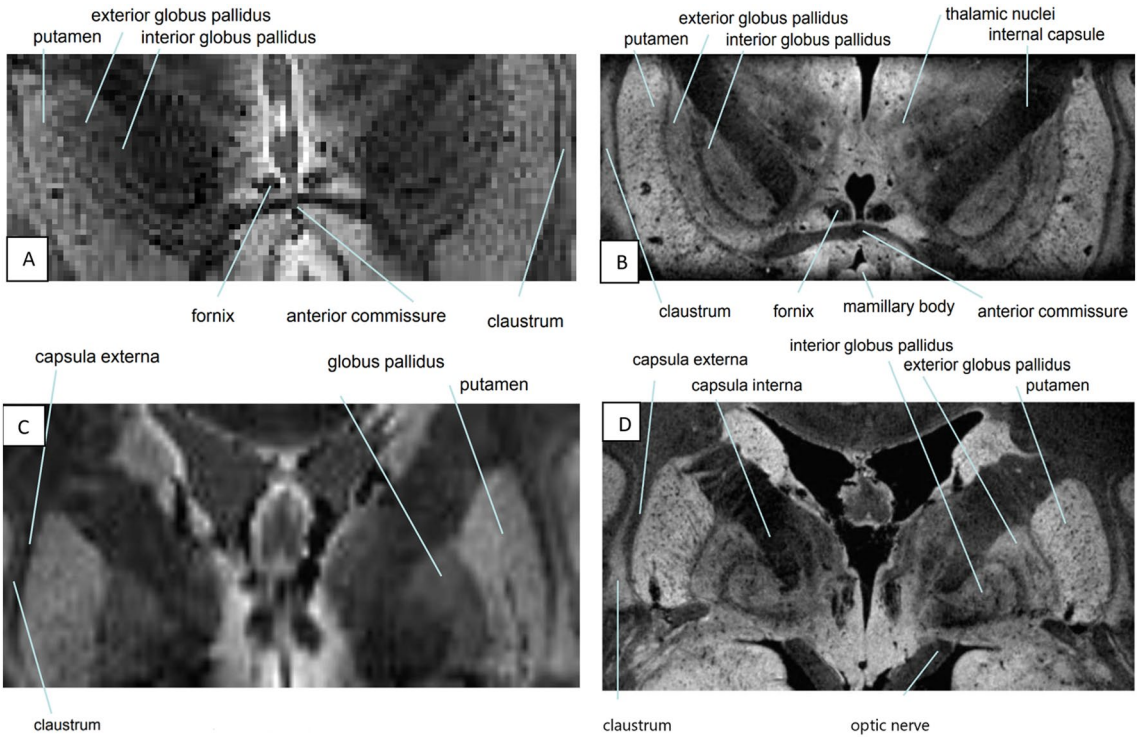

Fig. 2 3 T MR axial (**A**) and coronal (**C**) views of the basal ganglia [resolution; 600×600×600 μm^3]. Notice the additional structures visualized in the 9.4 T MR axial (**B**) and coronal (**D**) views [125× smaller voxels, resolution; 120×120×120 μm^3]. Image courtesy: Forschungszentrum Jülich

small-animal MRI system (BioSpec 70/30, Bruker, Germany) and biodistribution 64Cu or 68 Ga-labeled microspheres where PET provided a gold standard for MRI to validate imaging protocols [17]. The ultra-high-field PET/MR may act as a new tool for measuring glucose metabolism and related brain diseases or functional studies, such as Alzheimer's disease or memory and learning studies. Indeed, in a study conducted by Cho et al. to measure glucose metabolism in hippocampal substructures of five healthy volunteers through sequential FDG-PET and 7.0-T MR imaging, it was shown that the dentate gyrus and cornu ammonis had the highest glucose uptake [18]. Until recently, the resolving power of FDG-PET was inadequate for studying changes in glucose metabolism in hippocampal subdivisions of AD patients. However, using the High-Resolution Research Tomograph (HRRT; Siemens)-PET, a brain-dedicated system capable of imaging minute changes of chemicals, such as neurotransmitters and -receptors, with high sensitivity and spatial resolution, it is now possible to segment and assess glucose metabolism in the hippocampal subfields. Additionally, T2*-weighted MRI at 7.0 T allows the delineation of hippocampal substructures with higher definition, making hippocampal segmentation possible. Indeed, a study by Choi et al. used high-resolution FDG-PET and 7.0-T MRI (Siemens) to measure glucose metabolism in hippocampal subdivisions along the longitudinal axis of the hippocampus in early stage AD patients and healthy controls [19]. Additionally, in a study by Cho et al. where a PET/MRI system consisting of an HRRT and a 7.0-T MRI scanner was operated for in vivo visualization of thalamic subnucleus quantitative glucose metabolism, 7 T MR component scanner enabled in-detail discrimination of the thalamic nuclei, allowing precise localization of the corresponding in vivo metabolic activities obtained by the HRRT. This ultra-high-field PET/MR imaging system could be further useful in investigating mechanisms of pain or it could be extended to D receptor distribution in each thalamic nucleus and in the substantia nigra for imaging studies on Parkinsonian syndromes, and many more [20].

Furthermore, ultra-high-field PET/MRI has been shown to enable tracking of brain region-specific pathology in the context of AD, which may prove invaluable to understanding AD progression and therapeutic development. Indeed, in a study by Frost et al., fluorine-18 [^{18}F]-Florbetapir uptake in the 5×FAD brain by dedicated small-animal PET/MRI at 7.0 T and PET/CT were compared to validate the quantitative measurement of PET/MRI, since small-animal PET imaging is known to be limited by coarse spatial resolution. Interestingly, in addition to increased uptake in the cortex and hippocampus which are regions usually implicated in AD, their study demonstrated the highest uptake in the thalamus, a region overlooked in AD studies [21]. Interestingly, also a trimodal imaging system using the 9.4 T PET/MR integrated with EEG has been proposed, since the EEG signal covers the temporal aspect and can reflect functional changes allowing investigation of brain dynamics [23].

These are just a few studies to mention, since the novel ultra-high-field PET/MR systems have been commercially available only recently, and many more studies are yet to come with the adequate distribution of this ultra-high-field PET/MR facilities globally. If this tool is to have a widespread impact outside a small group of academic sites, training the next generation of technicians and interpreters remains one of the major challenges which will have to be met. According to Catana et al. [22], one of the main challenges, the limited space available inside the bore of standard MR systems to integrate the PET detectors, has been solved by introducing larger bore diameters that provided adequate space. However, we found no evidence explaining why ultra-high-field PET/MRI with large bore sizes for them to be used in the clinic is not yet available. We think that it has been due to the lack of adequate studies highlighting the clinical potential of this new multimodality imaging tool and possibly the technological challenges encountered in constructing integrated PET/MR systems at higher field strengths [23]. In addition, some other disadvantages of hybrid PET/MR technology are, for instance, longer acquisition protocols, higher scatter and attenuation due to head coils, the issue of attenuation correction, higher costs, etc., which have substantially slowed the development of clinical hybrid PET/MR systems [24–26]

In conclusion, more research is needed to determine the cost-effectiveness of PET-MR technology if it were to be used in day-to-day clinical practice. We are confident that it will be possible to translate these technologies used in preclinical studies at ultra-high-field strengths to guide research into similar human PET/MRI scanners through further technologic developments and appropriate modifications, which will lead the next generation of molecular imaging.

Data availability Not applicable.

Declarations

Conflict of interest The author has no conflicts of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Perera Molligoda Arachchige AS (2022) 7-Tesla PET/MRI: a promising tool for multimodal brain imaging? AIMS Neurosci 9(4):516–518. https://doi.org/10.3934/Neuroscience.2022029

2. Schütz L, Lobsien D, Fritzsch D, Tiepolt S, Werner P, Schroeter ML, Berrouschot J, Saur D, Hesse S, Jochimsen T, Rullmann M, Sattler B, Patt M, Gertz HJ, Villringer A, Claßen J, Hoffmann KT, Sabri O, Barthel H (2016) Feasibility and acceptance of simultaneous amyloid PET/MRI. Eur J Nucl Med Mol Imaging 43(12):2236–2243. https://doi.org/10.1007/s00259-016-3462-x
3. Sander CY, Hansen HD, Wey HY (2020) Advances in simultaneous PET/MR for imaging neuroreceptor function. J Cerebral Blood Flow Metab 40(6):1148–1166. https://doi.org/10.1177/0271678X20910038
4. Quick HH (2014) Integrated PET/MR. J Magn Reson Imaging JMRI 39(2):243–258. https://doi.org/10.1002/jmri.24523
5. Nensa F, Beiderwellen K, Heusch P, Wetter A (2014) Clinical applications of PET/MRI: current status and future perspectives. Diagn Interv Radiol (Ankara, Turkey) 20(5):438–447. https://doi.org/10.5152/dir.2014.14008
6. Son YD, Kim YB, Kim JH, Kim JH, Kwon DH, Lee H, Cho ZH (2022) Future prospects of positron emission tomography-magnetic resonance imaging hybrid systems and applications in psychiatric disorders. Pharmaceuticals (Basel, Switzerland) 15(5):583. https://doi.org/10.3390/ph15050583
7. Miller-Thomas MM, Benzinger TL (2017) Neurologic applications of PET/MR imaging. Magn Reson Imaging Clin N Am 25(2):297–313. https://doi.org/10.1016/j.mric.2016.12.003
8. Gsell W, Molinos C, Correcher C, Belderbos S, Wouters J, Junge S, Heidenreich M, Velde GV, Rezaei A, Nuyts J, Cawthorne C, Cleeren F, Nannan L, Deroose CM, Himmelreich U, Gonzalez AJ (2020) Characterization of a preclinical PET insert in a 7 tesla MRI scanner: beyond NEMA testing. Phys Med Biol 65(24):245016. https://doi.org/10.1088/1361-6560/aba08c
9. Pichler BJ, Judenhofer MS, Wehrl HF (2008) PET/MRI hybrid imaging: devices and initial results. Eur Radiol 18(6):1077–1086. https://doi.org/10.1007/s00330-008-0857-5
10. Hammer BE, Christensen NL, Heil BG (1994) Use of a magnetic field to increase the spatial resolution of positron emission tomography. Med Phys 21:1917–1920. https://doi.org/10.1118/1.597178
11. PET/MRI at 9.4T promises gains in neuroimaging. AuntMinnieEurope.com. Retrieved January 1, 2023, from https://www.auntminnieeurope.com/index.aspx?sec=ser&sub=def&pag=dis&ItemID=605236
12. Preclinical MRI 3T—4.7T—7T—9.4T—Variable field—cryogen-free. Retrieved January 1, 2023, from https://www.mrsolutions.com/mr-imaging/mr-imaging/mr-dry-magnet-cryogen-free/
13. Simultaneous PET/MR. Retrieved January 1, 2023, from https://www.bruker.com/en/products-and-solutions/preclinical-imaging/nmi/pet-insert.html
14. Viel T, Talasila KM, Monfared P et al (2012) Analysis of the growth dynamics of angiogenesis-dependent and -independent experimental glioblastomas by multimodal small-animal PET and MRI. J Nucl Med 53:1135–1145. https://doi.org/10.2967/jnumed.111.101659
15. Lohmann P, Werner JM, Shah NJ, Fink GR, Langen KJ, Galldiks N (2019) Combined amino acid positron emission tomography and advanced magnetic resonance imaging in glioma patients. Cancers 11(2):153. https://doi.org/10.3390/cancers11020153
16. Panebianco V, Giove F, Barchetti F et al (2013) High-field PET/MRI and MRS: potential clinical and research applications. Clin Transl Imaging 1:17–29. https://doi.org/10.1007/s40336-013-0004-4
17. Boś A, Bergmann R, Strobel K, Hofheinz F, Steinbach J, den Hoff JV (2012) Cerebral blood flow quantification in the rat: a direct comparison of arterial spin labeling MRI with radioactive microsphere PET. EJNMMI Res 2(1):47. https://doi.org/10.1186/2191-219X-2-47
18. Cho ZH, Son YD, Kim HK, Kim ST, Lee SY, Chi JG, Park CW, Kim YB (2010) Substructural hippocampal glucose metabolism observed on PET/MRI. J Nucl Med 51(10):1545–1548. https://doi.org/10.2967/jnumed.110.076182
19. Choi EJ, Son YD, Noh Y, Lee H, Kim YB, Park KH (2018) Glucose hypometabolism in hippocampal subdivisions in Alzheimer's disease: a pilot study using high-resolution 18F-FDG PET and 7.0-T MRI. J Clin Neurol (Seoul, Korea) 14(2):158–164. https://doi.org/10.3988/jcn.2018.14.2.158
20. Cho ZH, Son YD, Kim HK et al (2011) Observation of glucose metabolism in the thalamic nuclei by fusion PET/MRI. J Nucl Med 52:401–404. https://doi.org/10.2967/jnumed.110.081281
21. Frost GR, Longo V, Li T, Jonas LA, Judenhofer M, Cherry S, Koutcher J, Lekaye C, Zanzonico P, Li YM (2020) Hybrid PET/MRI enables high-spatial resolution, quantitative imaging of amyloid plaques in an Alzheimer's disease mouse model. Sci Rep 10(1):10379. https://doi.org/10.1038/s41598-020-67284-z
22. Catana C, Guimaraes AR, Rosen BR (2013) PET and MR imaging: the odd couple or a match made in heaven? J Nucl Med 54(5):815–824. https://doi.org/10.2967/jnumed.112.112771
23. Perera AS, Arachchige M (2023) Transitioning from PET/MR to trimodal neuroimaging: why not cover the temporal dimension with EEG? AIMS Neurosci 10(1):1–4. https://doi.org/10.3934/Neuroscience.2023001
24. Mayerhoefer ME, Prosch H, Beer L, Tamandl D, Beyer T, Hoeller C, Berzaczy D, Raderer M, Preusser M, Hochmair M, Kiesewetter B, Scheuba C, Ba-Ssalamah A, Karanikas G, Kesselbacher J, Prager G, Dieckmann K, Polterauer S, Weber M, Rausch I, Haug AR (2020) PET/MRI versus PET/CT in oncology: a prospective single-center study of 330 examinations focusing on implications for patient management and cost considerations. Eur J Nucl Med Mol Imaging 47(1):51–60. https://doi.org/10.1007/s00259-019-04452-y
25. Bogdanovic B, Solari EL, Villagran Asiares A, McIntosh L, van Marwick S, Schachoff S, Nekolla SG (2022) PET/MR technology: advancement and challenges. Semin Nucl Med 52(3):340–355. https://doi.org/10.1053/j.semnuclmed.2021.11.014
26. Choi C-H, Felder J, Lerche C, Shah NJ (2022) MRI coil development strategies for hybrid MR-PET systems: a review. IEEE Rev Biomed Eng. https://doi.org/10.1109/RBME.2022.3227337