FDOPA in Movement Disorders and Neuro-Oncology

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FDOPA Imaging for Neuro-oncology

Introduction

MRI is currently the modality of choice for diagnosing and monitoring brain tumors given its high resolution and excellent soft-tissue contrast. MRI is widely available and remains the mainstay for the initial clinical diagnosis, treatment planning, and posttreatment follow-up of brain tumors. A key feature of many high-grade gliomas is the compromise of the blood-brain barrier (BBB), which allows molecules, including intervenous CT and MR contrast, to enter the tumor but not enter a normal brain with an intact BBB. This compromise of the BBB can be detected as tumor enhancement on MRI through gadolinium-based contrast agent administration. However, many low-grade gliomas and some high-grade gliomas, mainly grade III, do not show contrast enhancement. Additionally, many high-grade gliomas that do show contrast enhancement also have substantial non-enhancing regions. Lack of contrast enhancement on MRI makes delineating tumor volumes and surgical margins much more challenging for surgical treatment planning and post-treatment follow-up of brain tumors. In addition, the ability of MRI to differentiate between treatment-induced changes and residual or recurrent tumor is also limited as the imaging features have substantial overlap [1].

Brain PET imaging with amino acid tracers has great potential to provide more accurate and informative imaging in neuro-oncology. MRI alone has limited accuracy for delineating tumor margins and poorly predicts the biological aggressiveness of gliomas, especially when tumors do not enhance with conventional gadolinium-based contrast agents. Several PET tracers have been used to study aspects of brain tumor metabolism [2–6], one of the first was 2-deoxy-2-^{18}F-fluoro-D-glucose (FDG), used to image glucose uptake and glycolytic metabolism. While there is some utility for brain tumor imaging using FDG-PET, there are limitations [7, 8] due to the high physiological glucose metabolism of normal gray matter, which results in modest FDG uptake of low-grade and some recurrent high-grade tumors making detection difficult [9]. Even in brain tumors visible on FDG-PET images, the high uptake of FDG in normal brain makes this tracer unsuitable for establishing tumor margins. Additionally, the specificity of FDG in tumor detection is often limited by uptake in non-tumor regions of inflammation [8, 10, 11].

Amino Acid Tracers in Neuro-oncology: FDOPA-PET

The PET tracer 3′-deoxy-3′-^{18}F-fluorothymidine (FLT) is used to image cellular proliferation and is more sensitive than FDG for detecting recurrent high-grade brain tumors due to the low background uptake of FLT in normal brain tissue. It has also been shown to correlate with the ex vivo Ki-67 proliferation marker and is an overall better prognostic marker of tumor progression and survival than FDG-PET [12]. However, FLT does not readily cross the intact BBB, limiting the evaluation of regions of tumors that do not enhance with contrast [13, 14]. Therefore, FLT is not well-suited to visualize the entire gross tumor volume or tumor margins when non-enhancing tumors are present.

Several amino acid PET tracers have established utility for imaging brain tumors, ^{11}C-methyl-L-methionine (MET), O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), and FDOPA [15–18]. These tracers target the system L substrates that are upregulated in tumors and do not depend on the BBB compromise [19, 20]. LAT1 expression has been shown to positively correlate with FDOPA uptake in resected glioma samples [20]. Unlike contrast-enhanced MRI, radiolabeled

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amino acid substrates transported by system L can visualize both contrast-enhancing and non-enhancing brain tumors [21, 22]. The two most widely used PET tracers for brain tumor imaging are MET and FET [23, 24]. MET is an essential amino acid-labeled carbon-11, and despite its efficacy, the short half-life of 20 minutes limits its use to sites with an in-house cyclotron facility. FET was developed in the late 1990s to provide an 18F-labeled amino acid PET tracer with a longer half-life (110 minutes) suitable for batch production and remote distribution. Studies directly comparing FET to MET for the characterization of brain tumors and differentiation of residual or recurrent tumor from treatment-related changes have shown these tracers to be very similar [24, 25].

FDOPA has been shown to have very similar brain tumor imaging properties to MET as expected from their shared transport mechanism. In a study directly comparing MET and FDOPA uptake in the same patients, mean tumor to contralateral SUV ratios were almost identical (2.05 for MET and 2.04 for FDOPA) [26]. In studies directly comparing FDOPA and FET, equivalent sensitivity was observed for high-grade and low-grade gliomas with no substantial difference in tumor uptake pattern seen [27, 28].

In the past several years, multiple studies have explored the use of FDOPA for imaging of newly diagnosed and previously treated brain tumors, including the comparison of FDOPA to MRI, FDG-PET, and MET-PET. In newly diagnosed patients, the sensitivity and specificity of FDOPA-PET in differentiating low-grade from high-grade tumors are similar to MET, varying from 70–96% and 86–100%, respectively, with FDOPA uptake correlating to the grade of the newly diagnosed glioma [21, 29–32]. The distinction of tumor recurrence or progression from radiation injury has been shown to be possible with the use of FDOPA with a sensitivity of 81.3% and specificity of 84.3% [33]. In a single study, FDOPA tracer uptake (SUV_{max}) correlated with tumor grade and proliferative activity only in untreated gliomas and not in previously treated gliomas [30]. In a head-to-head comparison, FDOPA is more accurate than FDG for imaging low-grade tumors, evaluating recurrent tumors, and distinguishing tumor recurrence from radiation necrosis [21, 34–36]. Compared to contrast-enhanced MRI, the accuracy of FDOPA-PET/CT was higher (97% vs. 80%, respectively) [17]. In a large comparative study with MRI, precise anatomic localization of FDOPA was facilitated by image fusion, with FDOPA-PET detecting both enhancing and non-enhancing tumors [37]. FDOPA has also been shown to be able to predict response in recurring malignant gliomas treated with bevacizumab [38]. A study of FDOPA-PET findings in gliomas correlated with histopathology-validated PET imaging showed that gliomas are underestimated by contrast-enhanced MRI and FDOPA more accurately delineate non-enhancing tumors [39]. This study also demonstrated the clinical utility of FDOPA-PET for guiding stereotactic biopsy by distinguishing areas of higher FDOPA uptake values. Better delineation of tumor margins is of considerable importance, given that gross total resection of gliomas is a primary goal of surgery and is associated with increased survival [40, 41].

The growing body of literature on amino acid PET tracers provides strong evidence of their significant clinical value in neuro-oncology by providing insights into the diagnosis and management of brain tumors and overcoming MRI limitations. Systemic reviews of the use of FDOPA-PET in diagnosing and managing primary brain tumors summarized the value of FDOPA as providing high diagnostic accuracy in the delineation of tumor extent, diagnosis of treatment-related changes, and assessment of treatment response [42, 43].

Image Interpretation

The diagnostic importance of amino acid PET is increasingly recognized and reflected in the response assessment in neuro-oncology (RANO) guidelines, which strongly recommended their use in brain tumor management [44], and by the joint practice guidelines collaboratively developed by the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Neuro-Oncology (EANO), and the working group for Response Assessment in Neuro-oncology with PET (PET-RANO) [45].

The visual assessment of FDOPA-PET images is to identify and locate areas of tracer uptake above the normal brain background using an appropriate color scale, set to the background counts in the lower third of the visual scale range. Standard summation (static) images are used for clinical reading and should be co-registered and fused with a recent high-resolution brain MRI if PET/MRI is not available. A positive FDOPA-PET scan is when the tracer uptake exceeds the background activity in the contralateral cortex. A negative scan is when no increased uptake above background is identified.

The recommended approach for a semi-quantification analysis to measure tracer uptake is performed by calculating the tumor to striatum ratio (TSR) using mean SUV (TSR_{mean}) and maximum SUV (TSR_{max}) values, respectively. The guidelines note that FDOPA TSR cutoff thresholds for the definition of biological tumor volume have not been validated for all clinical questions.

Currently, there are no established guidelines for processing and determining clinical values using dynamic FDOPA-PET acquisitions.

Clinical Application in Neuro-oncology and PET/MRI

In clinical practice, one of the key utilizations of the hybrid modality PET/MR is in neuro-oncology, given that MRI is the modality of choice for diagnosing and monitoring brain tumors, and PET provides complementary functional information. One of the most successful PET/MRI applications has been in pediatric oncology, providing multiple benefits to these patients by offering a reduction in the total number of imaging studies and necessary sedations, decreasing radiation exposure, and the potential adverse long-term effects from sedation and radiation due to serial imaging. Taken together, the advantages of simultaneous brain PET/MR imaging and a growing list of PET tracers have great potential to significantly improve and simplify patient management in neuro-oncology.

Pediatric and adult brain tumor treatment commonly includes antiangiogenic drugs such as bevacizumab, a humanized anti-VEGF monoclonal antibody. Bevacizumab treatment results in an early decrease in contrast enhancement, which creates problems for imaging evaluation since this apparent decreased vascular permeability and enhancement does not correlate with decreased tumor viability in this setting. Recently, simultaneous FDOPA-PET/MRI was used to monitor the effects of antiangiogenic therapy with bevacizumab in pediatric patients with recurrent gliomas and suggested that FDOPA may better predict response at 3 months after initiating therapy than MRI alone [46].

In this study, tumors were readily visualized with FDOPA-PET/MRI on the baseline study prior to therapy with bevacizumab. The metabolic tumor volume (MTV), defined by a 1.5-fold threshold based on the normal contralateral side uptake, decreased in all patients by varying amounts. After 4 weeks of bevacizumab therapy, the largest MTV decrease was 2% of the baseline MTV (Fig. 13.1) and the smallest decrease was 77% of baseline (Fig. 13.2). Patients with a smaller baseline decrease in MTV had worst clinical outcomes. One patient had two distinct lesions with variable response to therapy; the optic chiasm tumor baseline decrease in MTV was 33%, while that of the optic nerve glioma was 56% (Figs. 13.3 and 13.4).

Studies using simultaneous FDOPA-PET/MRI images have shown more accurate tumor visualization and delineation in gliomas, and the FDOPA-PET tumor region extended beyond the area defined by T1-weighted contrast enhance-

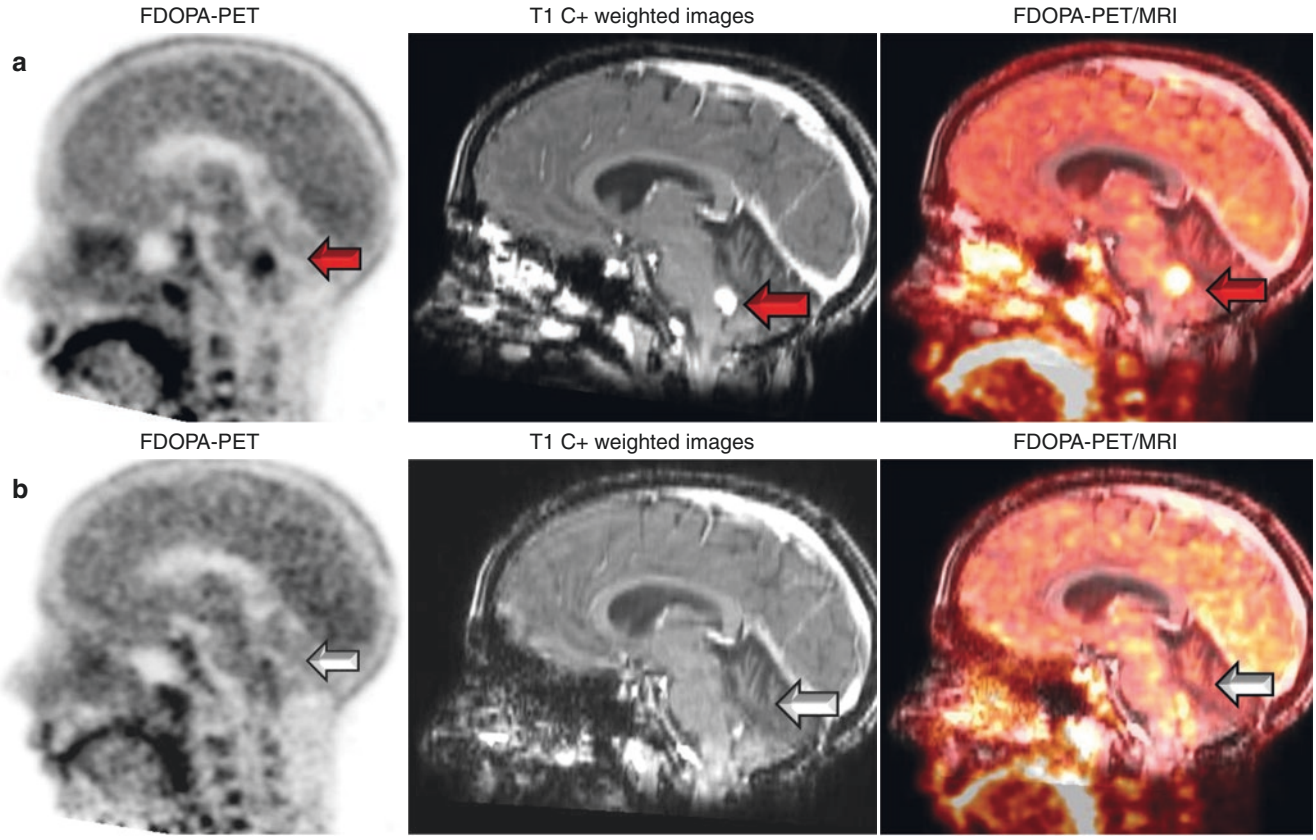

Fig. 13.1 FDOPA-PET/MRI in a pediatric patient with cerebellar pilocytic astrocytoma. Images obtained prior to therapy (**a**, red arrows) and after 4 weeks of bevacizumab therapy (**b**, white arrows). There is near-complete resolution of the metabolic tumor volume (MTV), with 2% remaining

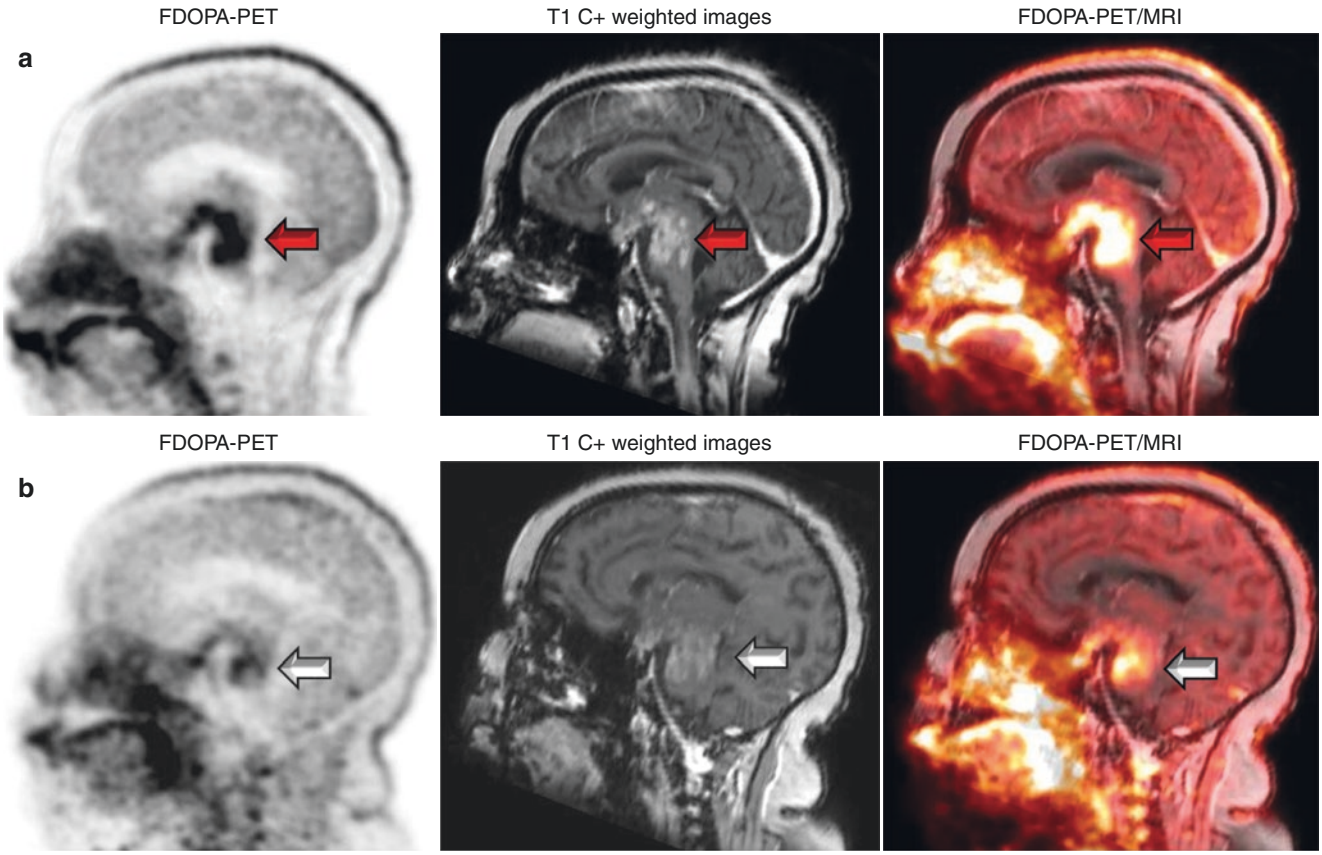

Fig. 13.2 FDOPA-PET/MRI in a pediatric patient with grade IV small-cell astrocytoma. Images obtained prior to therapy (**a**, red arrows) and after 4 weeks of bevacizumab therapy (**b**, white arrows). There is a small decrease of the metabolic tumor volume (MTV), with 77% remaining

ment and was variable in size to the area of T2/FLAIR hyperintensity (Figs. 13.5 and 13.6) [47, 48]. One study also integrated imaging findings with biopsy locations, histopathology, and established molecular markers in gliomas and noted that it impacted patient management [47], shown in Figs. 13.7, 13.8, and 13.9.

FDOPA Imaging for Dopaminergic System

Introduction

The dopaminergic system is associated with numerous neurological disorders (Parkinson's disease, Huntington's disease, tardive dyskinesia) and psychiatric disorders (depression, addiction, and schizophrenia), given the significant role it plays in several functions, including motor, memory, cognition, and emotions. Parkinson's disease (PD) is a chronic neurodegenerative disorder clinically characterized by asymmetric parkinsonism (bradykinesia, tremor, rigidity, and postural instability) and progressive loss of dopamine neurons in the midbrain with resulting dopaminergic deafferentation of the basal ganglia [49]. The pathological hallmarks of PD are degeneration of the nigrostriatal dopaminergic system and the presence of Lewy bodies and neurites, intracellular inclusions of aggregated α-synuclein, and other proteins such as ubiquitin [50]. Parkinsonian syndromes are a group of disorders that shared the clinical signs of PD but are considered separate conditions based on their different pathologies. Atypical parkinsonism syndromes are other neurodegenerative diseases associated with parkinsonism, and the most common being multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies (DLB). These conditions are linked with nigrostriatal degeneration, a type of multiple system atrophy. Clinical manifestations of parkinsonism may also be seen by syndromes not associated with nigrostriatal degeneration, such as essential tremor, drug-induced parkinsonism, and vascular parkinsonism [51]. Moreover, difficulties are associated with the clinical differentiation of patients with parkinsonism with dementia from Alzheimer's disease, given the overlapping features [52].

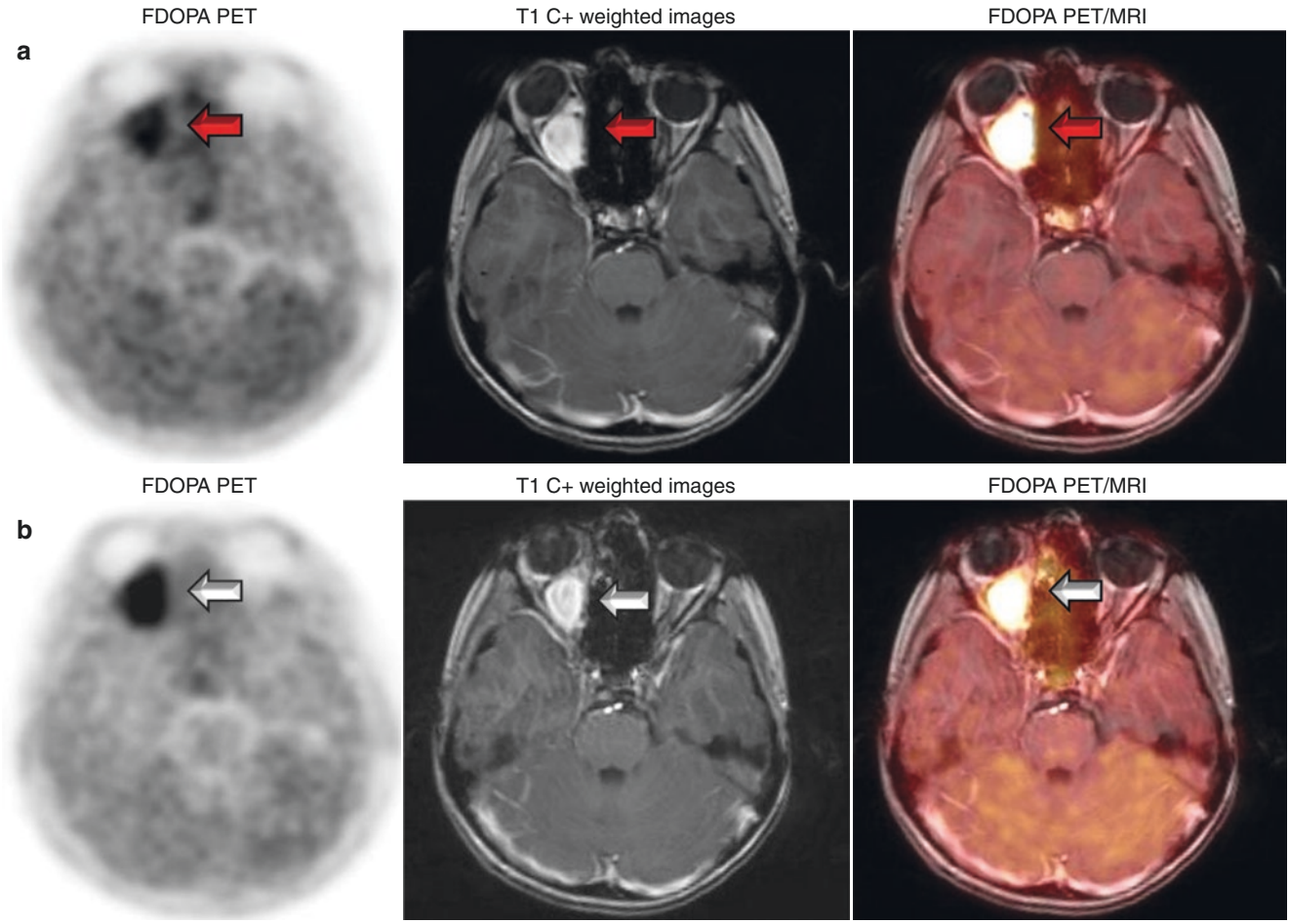

Fig. 13.3 FDOPA-PET/MRI in a pediatric patient with two distinct tumors with variable response to therapy. Images of the optic nerve glioma obtained prior to therapy (**a**, red arrows) and after 4 weeks of bevacizumab therapy (**b**, white arrows). There is a moderate decrease of the metabolic tumor volume (MTV), with 56% remaining

Dopamine PET-Ligands

Functional imaging with dopamine PET-ligands is used to assess dopamine synthesis, transport, and receptor densities and is performed using single-photon emission computed tomography (SPECT) or PET [53]. These imaging agents can target either presynaptic dopamine transporter and synthesis or postsynaptic D2 dopamine receptors [54]. As an example, we focus here on the PET tracer, FDOPA, which is widely used for presynaptic dopaminergic imaging to distinguish between the different causes of parkinsonism and neurodegenerative versus non-dopamine deficiency etiologies [55, 56]. FDOPA is approved by the European Medicines Agency (EMA) for assessing dopaminergic neuronal integrity in suspected parkinsonian syndromes, and in October 2019, a US academic medical center received US Food and Drug Administration (FDA) approval to manufacture FDOPA for clinical use [57]. Studies have demonstrated that FDOPA-PET scans are able to diagnose presynaptic dopaminergic deficits in early phases of PD with excellent sensitivity and specificity [58].

An accurate diagnosis of PD is a prerequisite for patient management, given that only PD patients clinically respond to antiparkinson drug therapy. Neuroimaging has played an increasingly important role in the differential diagnosis, and various imaging modalities have been used to confirm PD or rule out other parkinsonian syndromes. For example, FDOPA-PET may be used to differentiate LB-type dementias (PD and DLB) from non-LB dementias, such as AD, based on the determination of nigrostriatal degeneration, in which the midbrain striatal uptake becomes more visible due to global reduction of striatal FDOPA uptake [59]. The accurate diagnosis among parkinsonism variants remains challenging using neuroimaging, particularly in the early or mild stages of the disease. Multiple investigators have reported minimal differences in the reduction of FDOPA uptake between PD and parkinsonian syndromes associated with nigrostriatal degeneration, given the overlap between these

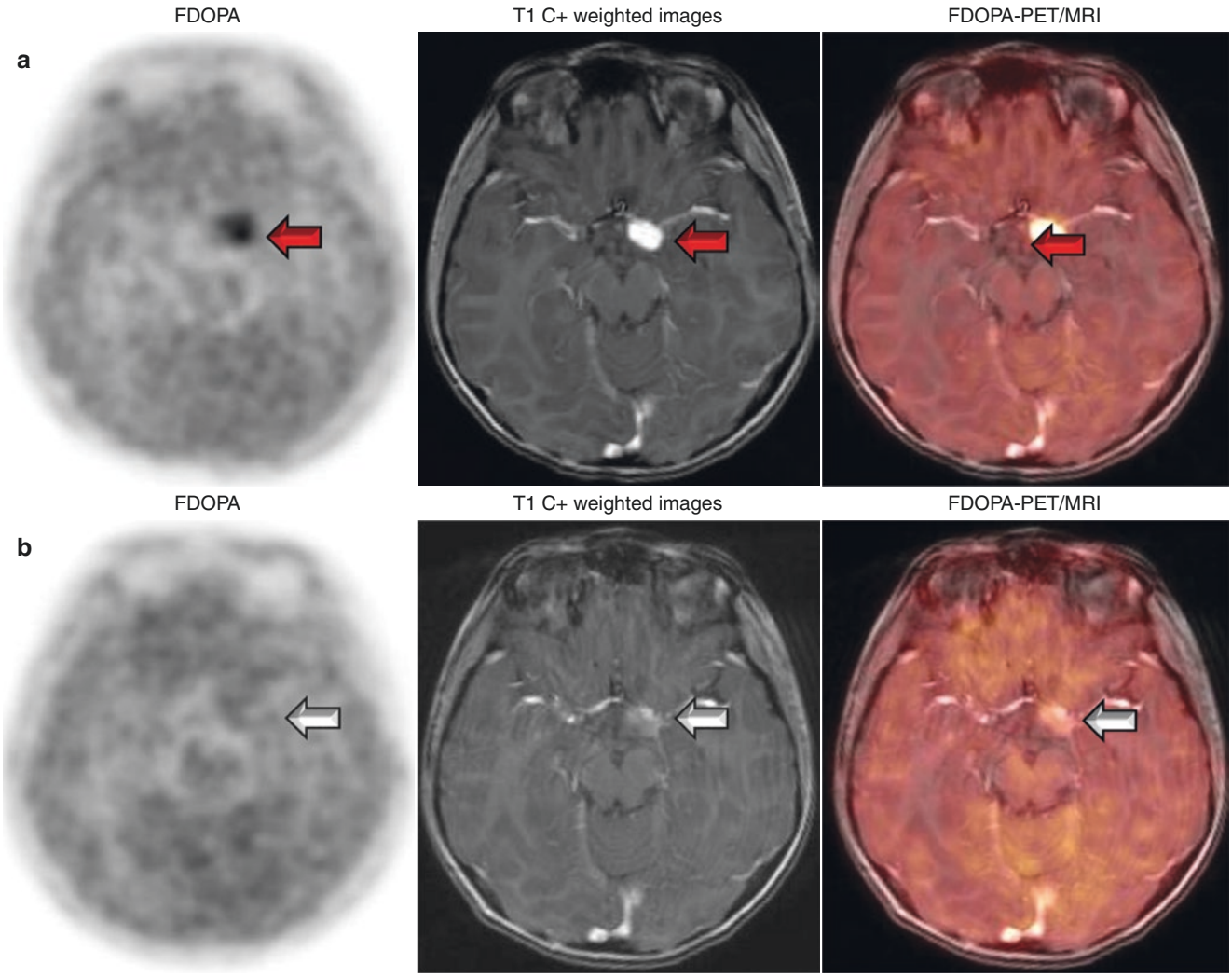

Fig. 13.4 FDOPA-PET/MRI in a pediatric patient with two distinct tumors with variable response to therapy. Images of the optic chiasm glioma obtained prior to therapy (**a**, red arrows) and after 4 weeks of bevacizumab therapy (**b**, white arrows). There is a significant decrease of the metabolic tumor volume (MTV), with 33% remaining

populations [60, 61]. FDOPA-PET is normal in essential tremor, drug-induced parkinsonism, and psychogenic parkinsonism since these disorders are not associated with pathologic dopaminergic loss [62–64].

Neuroimaging with FDOPA-PET has been applied to psychiatric disorders evaluating presynaptic dopaminergic integrity. In a study on depression, FDOPA uptake in the left caudate was significantly lower in depressed patients with psychomotor retardation than in normals, providing direct evidence of a link between dopamine hypofunction and psychomotor retardation in depression [65]. Increased striatal FDOPA accumulation has been reported in patients with psychosis, suggesting an increased synthesis and dopamine turnover in these patients [66]. Increased FDOPA uptake was also noted in patients who responded to classic antipsychotics, but not in patients with treatment-resistant schizophrenia, suggesting that dopamine synthesis capacity may be a useful biomarker to predict treatment responsiveness [67]. Several studies have used FDOPA-PET to evaluate dopamine's role in the human reward system [68] and to assess aging effects and cognitive functions [69], given that reward processing is particularly vulnerable to aging.

Image Interpretation

The EANM and the SNMMI have developed practice guidelines that address dopaminergic imaging's clinical and technical aspects in parkinsonian syndromes [70]. The diagnostic importance of presynaptic dopaminergic imaging using FDOPA-PET is for detecting loss of nigrostriatal dopaminergic neuron terminals in patients with parkinsonian syndromes. The visual assessment goal is to identify and locate areas of striatal uptake (putamen and caudate nucleus) using an appropriate color scale by setting the maximum color scale value to the maximal tracer value within the striatum. A

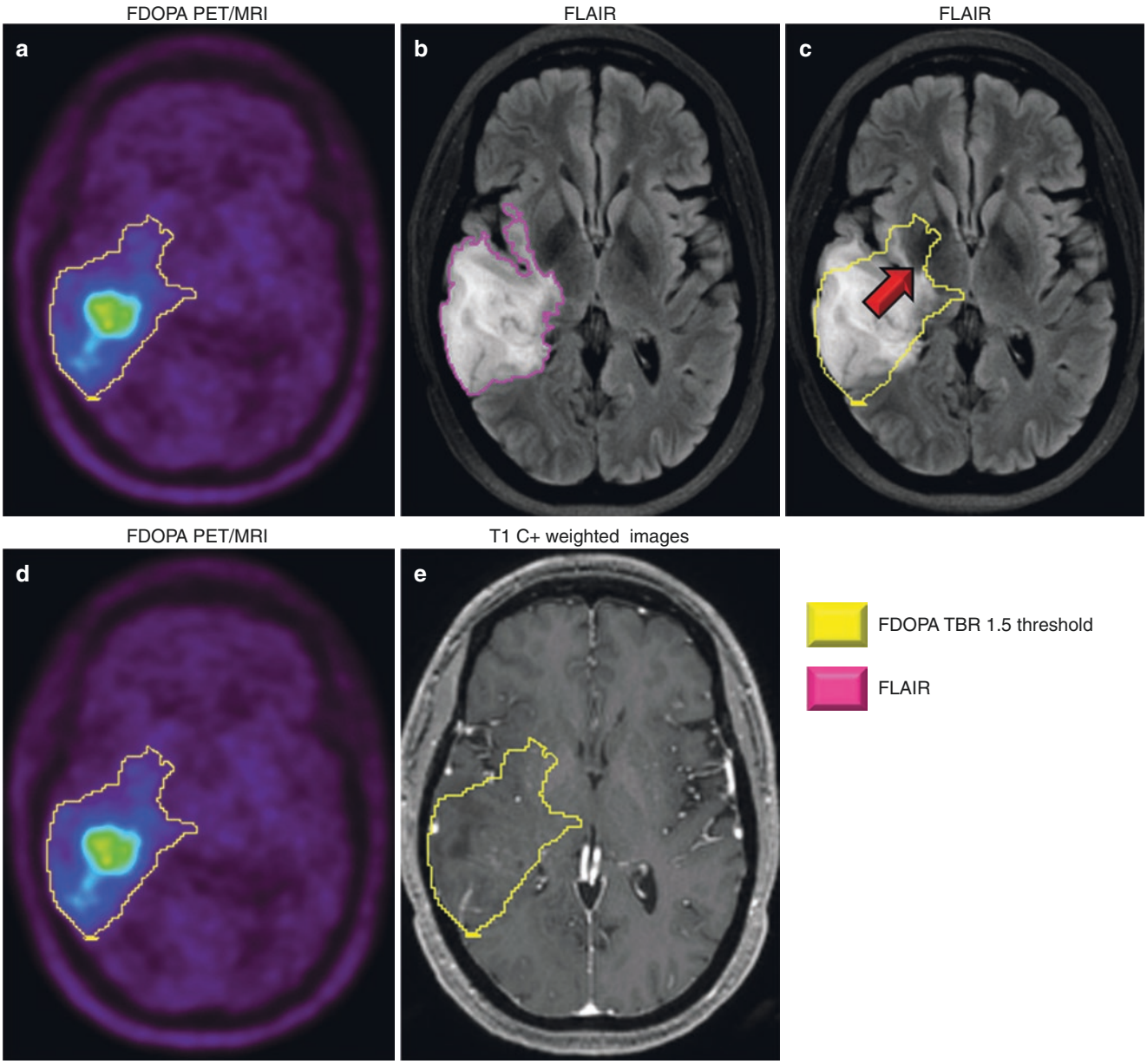

Fig. 13.5 FDOPA-PET/MRI in an adult patient with anaplastic oligodendroglioma grade III, Ki-67 of 80–90%. (**a**) FDOPA contour representing the region of tumor uptake based on the tumor to normal brain ratio (TBR) > 1.5 (yellow outline). (**b**) FLAIR contour delineating the region of hyperintensity (magenta outline). (**c**) TBR contour superimposed on T2/FLAIR illustrates that tumor uptake extends beyond the T2/FLAIR abnormalities (red arrow). (**d** and **e**) TBR contour superimposed on T1-weighted MR with contrast. FDOPA-PET demonstrates higher sensitivity than MR T1-weighted with contrast and T2/FLAIR signal intensity abnormalities to delineate the non-enhancing tumor. (Courtesy of Dr. Jonathan McConathy, Director, Division of Molecular Imaging and Therapeutics, The University of Alabama at Birmingham, Birmingham, Alabama, United States)

semi-quantification approach of tracer uptake is performed by calculating the striato-occipital ratio (SOR) [71], which has been shown to detect subtle asymmetric putamen FDOPA reductions and correlate SOR with ratings of disability. Analysis of dynamic FDOPA-PET time-activity curves (TACs) has been used to quantify and model multiple aspects of FDOPA influx constants (Ki maps) [58].

Visual Assessment

In a negative dopaminergic imaging PET scan, the normal striata show a comma-shaped with symmetric well-delineated borders on axial images with the maximum uptake corresponding to the putamen. Mild asymmetry may occur in normal subjects.

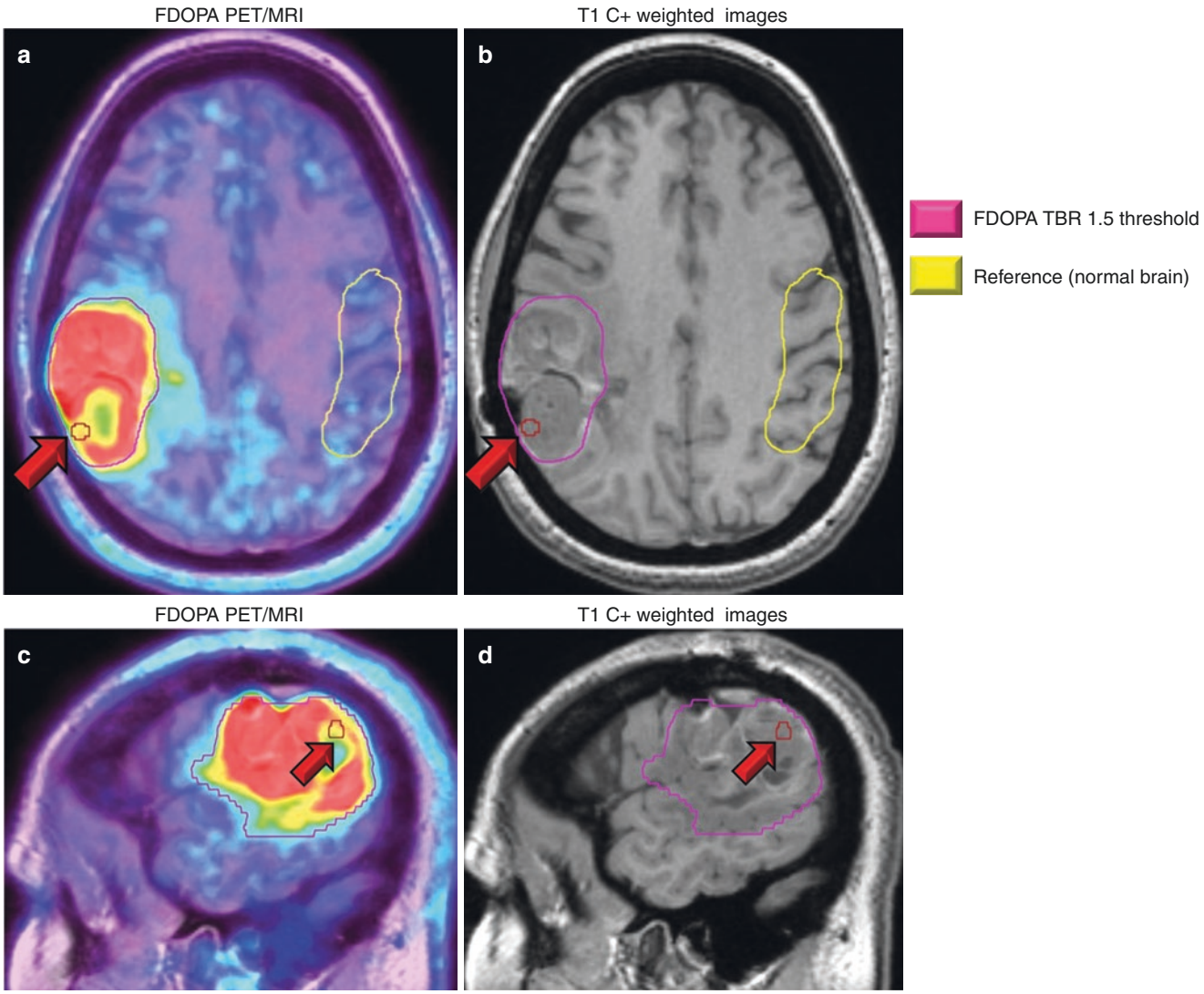

Fig. 13.6 FDOPA-PET/MRI in an adult patient with anaplastic oligodendroglioma, WHO grade III, Ki-67 of 80–90%. (**a** and **c**) FDOPA contour represents the region of tumor uptake based on the tumor to normal brain ratio (TBR) > 1.5 (magenta outline). (**b**–**d**) TBR contour superimposed on T1-weighted MR with contrast. Contralateral normal brain used as the reference region (yellow outline). MRI T1-contrast does not reliably reflect areas of viable brain tumor. The FDOPA-PET impacted the selection of biopsy sites and resection. (**a**–**d**) Red arrows indicate the stereotactic biopsy sites

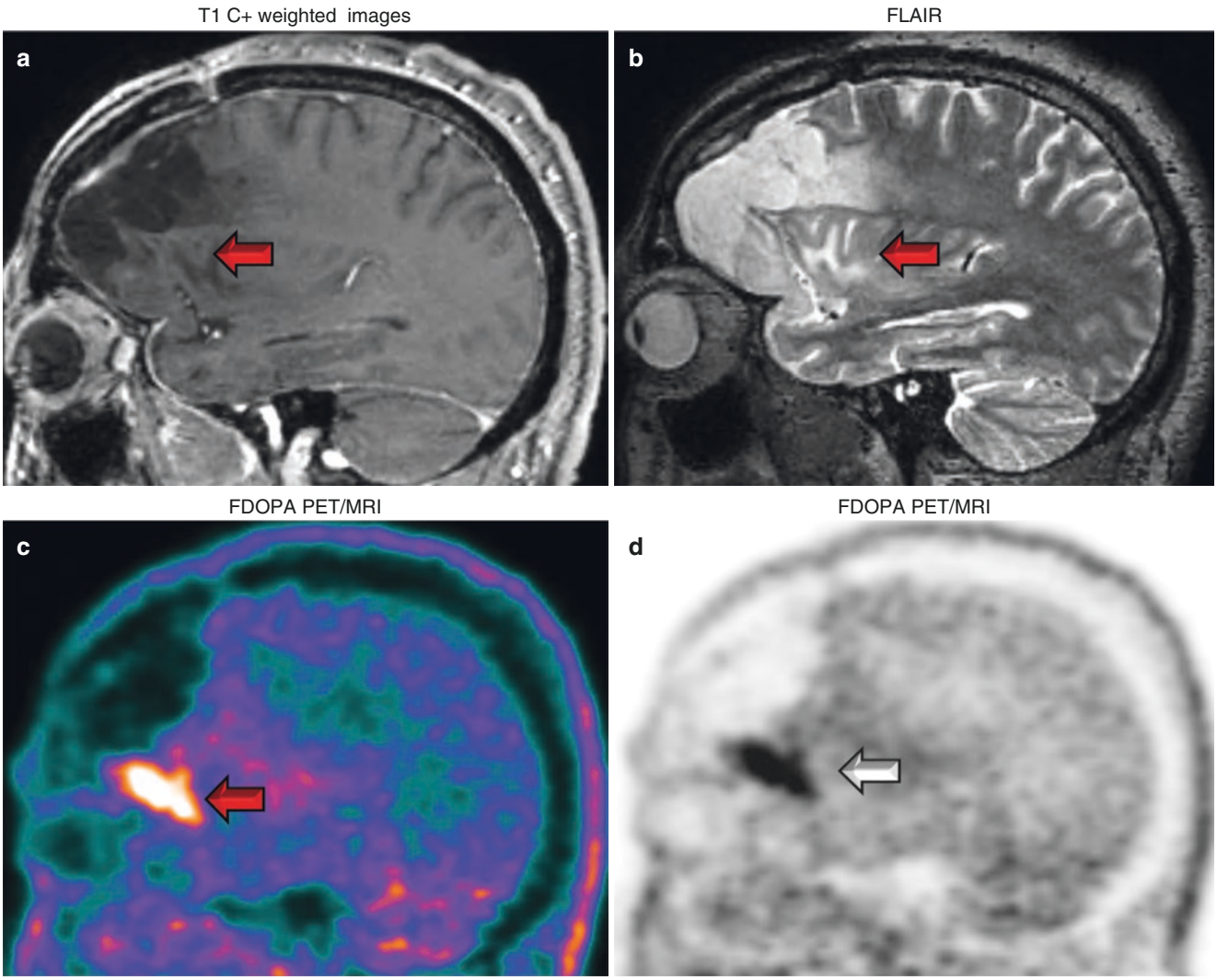

Fig. 13.7 FDOPA-PET/MRI in an adult patient was recurrent anaplastic astrocytoma, WHO grade III, Ki-67 of 10.5%. (**a** and **b**) Left frontal non-enhancing and T2/FLAIR hyperintensity that was initially reported as stable post-treatment changes (red arrows). (**c** and **d**) Marked focal increased FDOPA avidity (white arrows) in the follow-up of previously treated astrocytoma, consistent with tumor recurrence. FDOPA-PET/MRI was more accurate than MRI alone in distinguishing between tumor recurrence and radiation necrosis

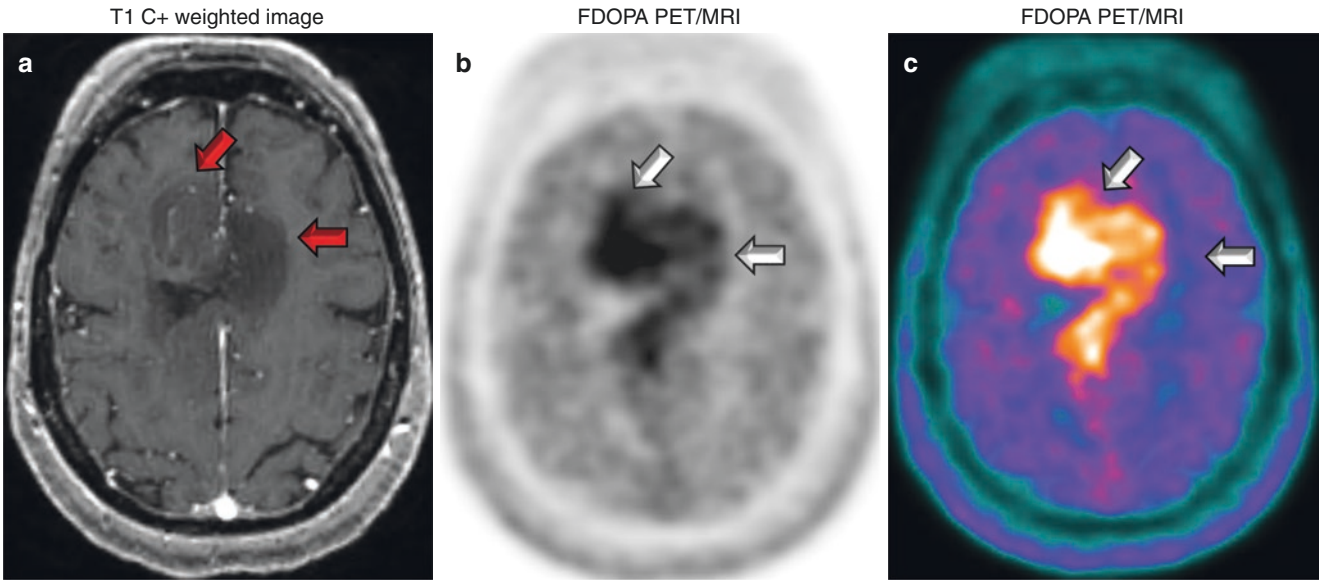

Fig. 13.8 FDOPA-PET/MRI in an adult patient with oligodendroglioma, WHO grade II, Ki-67 of 4.7%. (**a**) Minimally non-enhancing frontal mass (red arrows). (**b** and **c**) Marked FDOPA uptake in the tumor. The delineated FDOPA tumor margins impacted radiotherapy target volumes

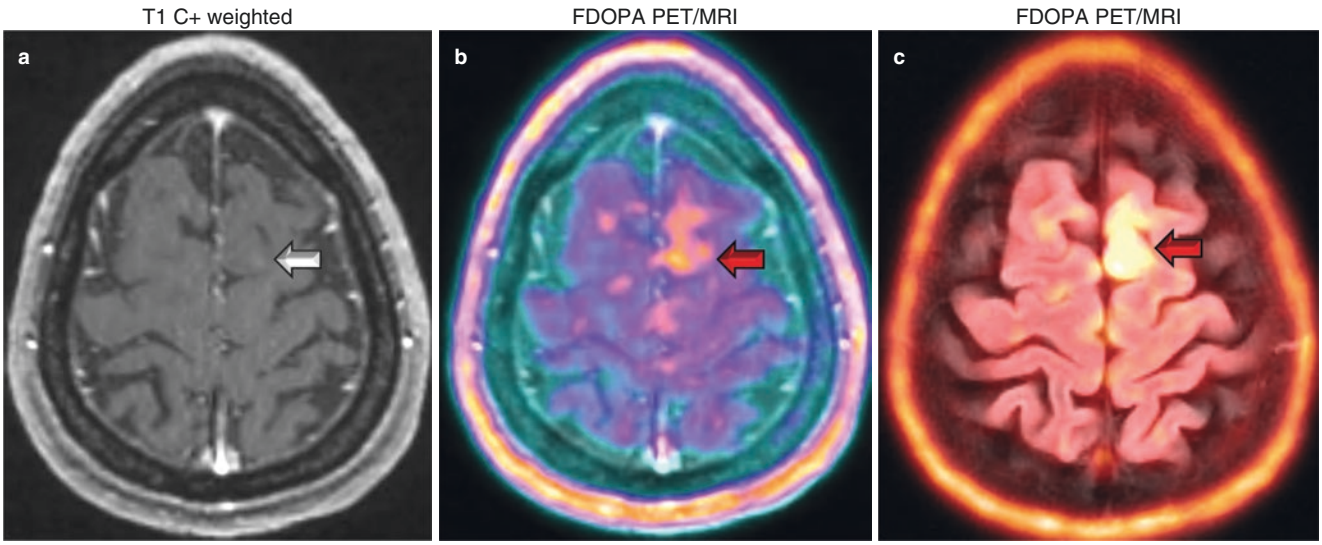

Fig. 13.9 FDOPA-PET/MRI in an adult patient with oligodendroglioma, WHO grade II, Ki-67 of 4.8%. (**a**) Minimal, non-enhancing left frontal lesion (white arrow). (**b** and **c**) Moderate FDOPA avid lesion (red arrows). The FDOPA has better detection of the tumor than MRI

In a positive dopaminergic imaging PET scan, there is a decreased tracer uptake on one or both striata, with an oval or circular shape. An asymmetric pattern of reduced putamen and preserved caudate uptake showing a caudate to putamen posterior-anterior gradient or dot shape is most consistent with parkinsonism syndromes (Fig. 13.10). The locus coeruleus and substantial nigra nuclei may become more visible in nigrostriatal degeneration cases (Figs. 13.11 and 13.12).

Role of PET/MRI Dopaminergic System Imaging

The introduction of simultaneous PET/MRI in the field of movement disorders is still in the early stages. Recent studies [72–74] have focused on better characterization of parkinsonism using PET/MRI. Structural findings on MRI, namely lacunar infarcts or enlarged perivascular spaces found in the basal ganglia and midbrain, may aid in improving PET assessment.

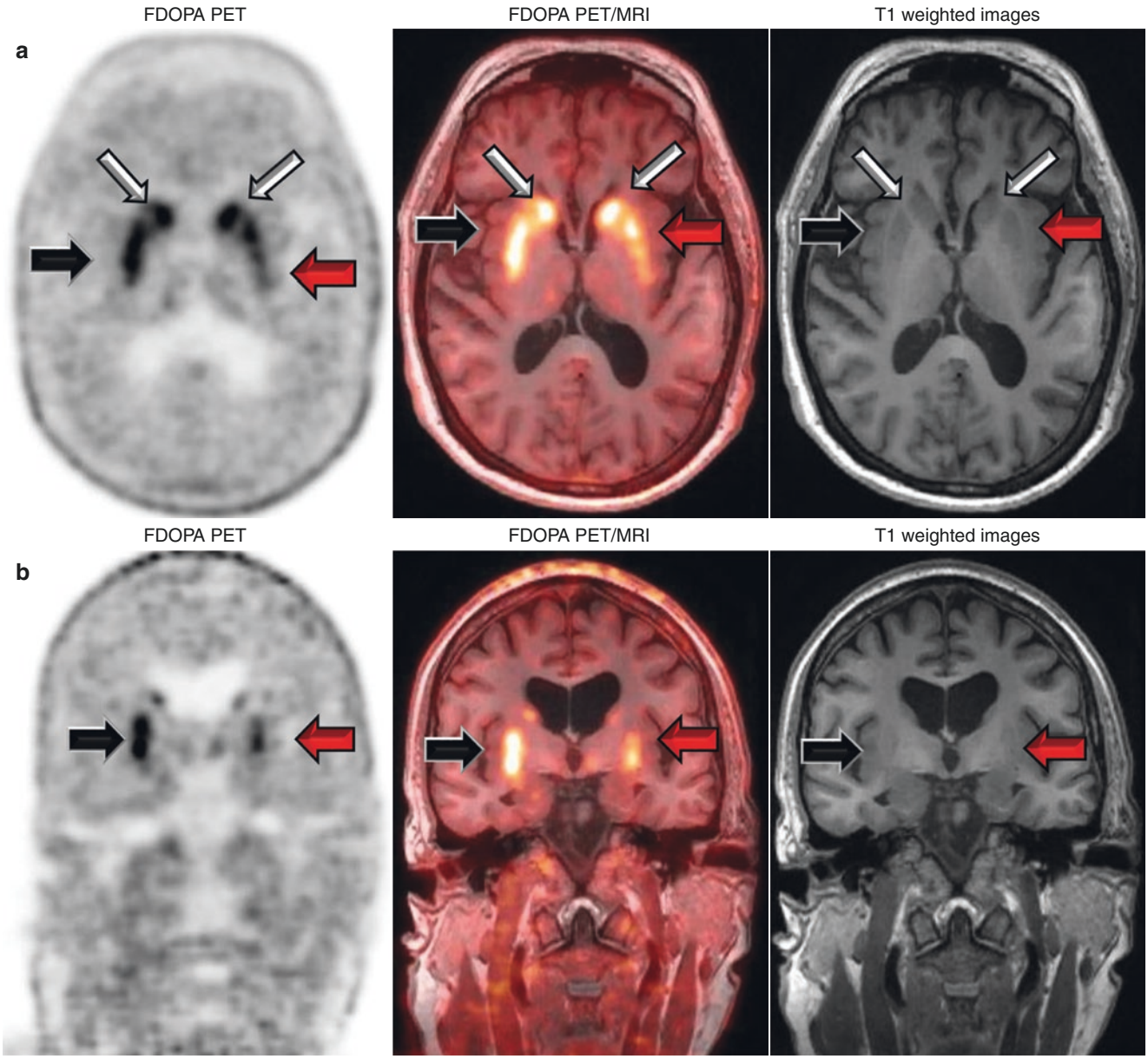

Fig. 13.10 FDOPA-PET/MRI demonstrates a positive dopaminergic imaging PET scan. The (**a**) axial images and (**b**) coronal images show asymmetric reduced tracer uptake in the putamen, more pronounced in the posterior part creating a posterior-anterior gradient (read arrows) with preserved bilateral tracer uptake in the caudate (white arrows) and right putamen (black arrows). (Courtesy of Dr. Juan M. Chomont, Chief of Radiology at INTECNUS, S.C. de Bariloche, Argentina)

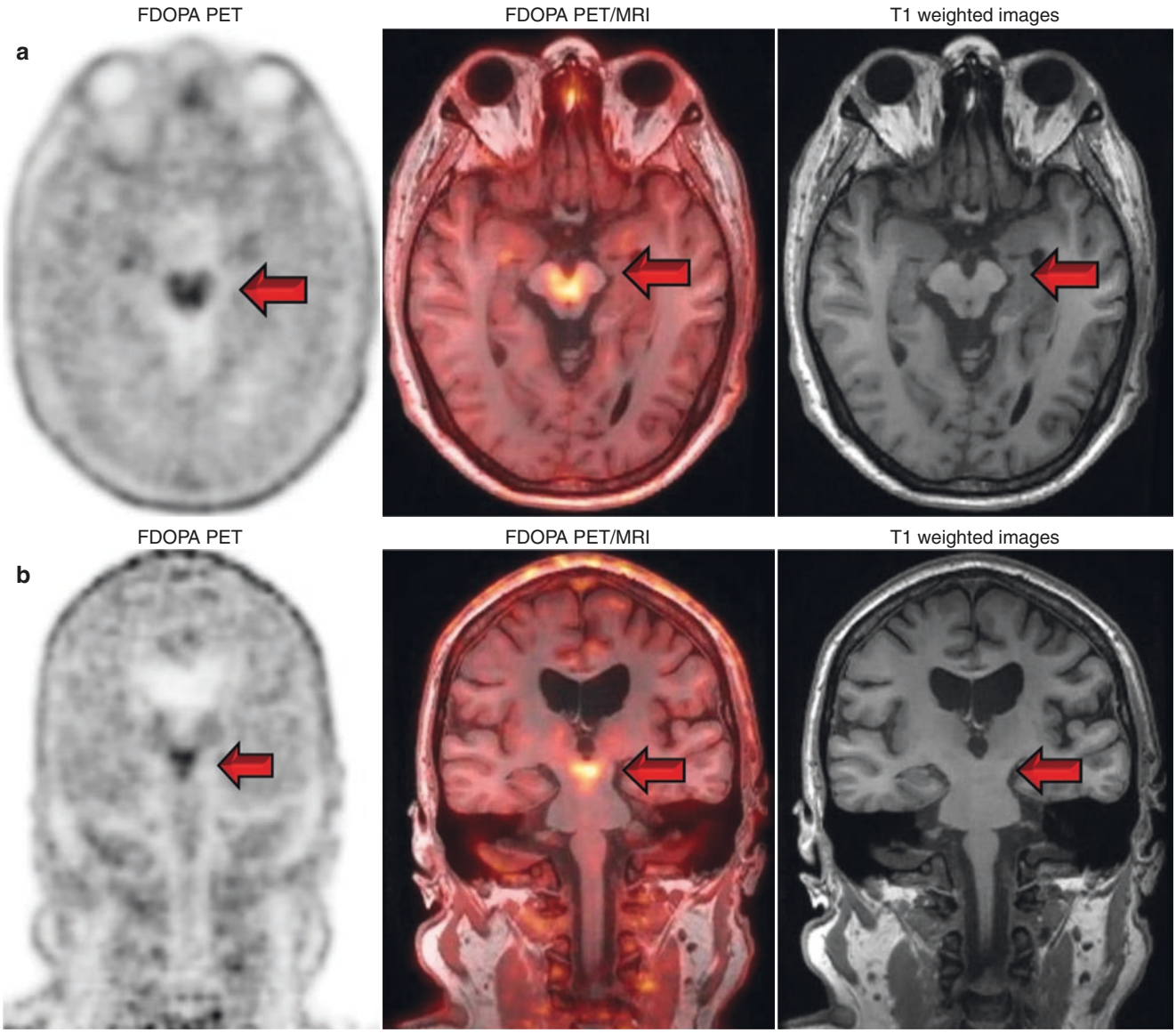

Fig. 13.11 FDOPA-PET/MRI demonstrates extrastriatal mesencephalic uptake in a patient with nigrostriatal degeneration in the (**a**) axial images and (**b**) coronal images (red arrows). (Courtesy of Dr. Juan M. Chomont, Chief of Radiology at INTECNUS, S.C. de Bariloche, Argentina)

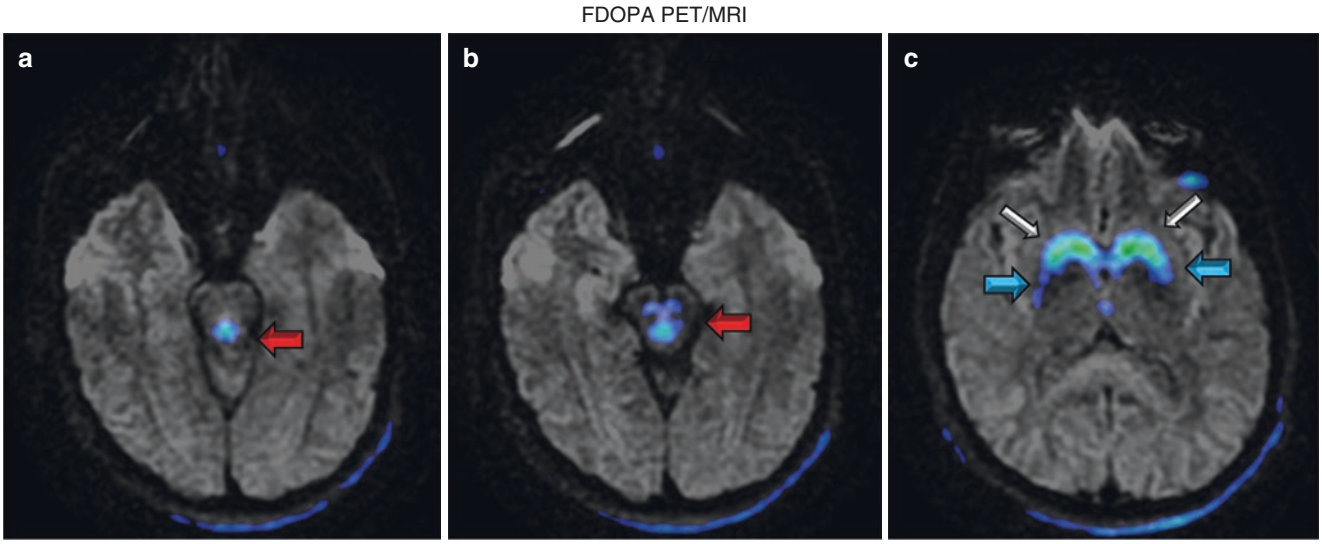

Fig. 13.12 FDOPA-PET/MRI demonstrates locus coeruleus and substantia nigra tracer uptake in a patient with severe nigrostriatal degeneration (**a** and **b**: red arrows). Marked bilateral putaminal reduction in tracer binding (**c,** blue arrows) and normal caudate uptake (**c,** white arrows). (Courtesy of Dr. Juan M. Chomont, Chief of Radiology at INTECNUS, S.C. de Bariloche, Argentina)

These lesions, best identified on MRI, cause decreased striatal uptake depending on their location, mimicking PET features of PD and provide alternative etiologies for the patient's symptoms.

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