Brain ^{18}F-FDG-PET: Utility in the Diagnosis of Dementia and Epilepsy

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ABSTRACT: The authors reviewed the two most common current uses of brain ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) at a large academic medical center. For epilepsy patients considering surgical management, FDG-PET can help localize epileptogenic lesions, discriminate between multiple or discordant EEG or MRI findings, and predict prognosis for post-surgical seizure control. In elderly patients with cognitive impairment, FDG-PET often demonstrates lobar-specific patterns of hypometabolism that suggest particular underlying neurodegenerative pathologies, such as Alzheimer's disease. FDG-PET of the brain can be a key diagnostic modality and contribute to improved patient care.

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KEY WORDS: ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET), Alzheimer's disease, dementia, epilepsy

Recent technological advances in the resolution of positron emission tomography (PET) systems and commercial image analysis software have resulted in the increased use of molecular imaging techniques, such as measurement of glucose uptake and metabolism with ^{18}F-labeled fluoro-2-deoxyglucose (FDG). Brain FDG-PET has potentially important roles for the imaging evaluation of patients with brain tumors, epilepsy, and dementia syndromes. FDG-PET can increase early recognition of underlying neurodegeneration in patients with subtle signs and symptoms of cognitive impairment before the onset of debilitating dementia. FDG-PET is used in patients with medically refractory partial epilepsy for sensitive detection of the epileptogenic lesion and surrounding seizure network. FDG-PET can help improve diagnostic clarity in patients with confusing or nondiagnostic electroencephalogram (EEG), and in patients with normal magnetic resonance imaging (MRI) or MRI that identifies multiple potential epileptogenic lesions.

FDG-PET PROVIDES WELL-VALIDATED KEY VALUE TO DEMENTIA DIAGNOSIS AND PROGNOSIS AND SHOULD BE CONSIDERED AS ONE OF THE MOST VALUABLE TOOLS FOR MONITORING NEURODEGENERATIVE DISEASE STATUS AND PROGRESSION

In this review we discuss recent literature in the context of our clinical experience of brain FDG-PET and its application to dementia and epilepsy. We provide several key illustrative imaging examples. With the increasing use of integrated PET-MRI in clinical practice, our primary aim was to increase familiarity and confidence for radiology trainees and faculty to safely perform and correctly interpret brain FDG in their clinical practice.

FDG MECHANISM AND METABOLISM

PET utilizes biologically active molecules in micromolar or nanomolar concentrations that have been labeled with short-lived positron-emitting radioisotopes that are introduced intravenously into the body [1]. Since its introduction in 1976, FDG, as a biomarker of glucose metabolism, has become the most widely used PET probe in clinical practice (~90%) [2].

FDG is a glucose analog radiopharmaceutical that has a half-life of 110 minutes and is commonly used for studying brain glucose metabolism. FDG is transported from the blood into cells by glucose transporters, predominantly GLUT1. Once in the cell, it is phosphorylated by hexokinase to form FDG-6-phosphate. Further metabolism of FDG-6-phosphate is limited and it is essentially trapped intracellularly.

Glucose is the primary source of energy in the adult brain, and therefore it demonstrates intense FDG uptake, particularly in the cortex and deep gray matter structures, (2 to 4 times higher than normal white matter in resting conditions). Local glucose consumption, and thus FDG cerebral uptake, is closely coupled to neuronal function, and proportionally increases with stimulus intensity and frequency, and decreases in conditions of sensory deprivation [3]. Such metabolic variations occur at the level of synaptic connections.

FDG uptake in the brain is generally considered homogeneous and symmetrical, with some exceptions. Cortical asymmetries in FDG uptake have been observed in the inferior parietal lobule structures (including Wernicke's region), orbitofrontal gyri and anteromedial temporal cortices, with

maximum variance of approximately 10% [4]. FDG uptake is usually higher in the frontal, parietal, and occipital areas compared to the temporal cortex, while the basal ganglia have slightly higher activity than the cortex. Global cerebral metabolic rates of glucose inversely correlate with age, with a reported decline of 12–13% for people approximately 20 years of age compared to those older than 70 years [5]. The most common metabolic reductions with advanced age have been observed in the frontal lobes, particularly the anterior cingulate cortex, dorsolateral and medial prefrontal cortices, and orbitofrontal cortex, bilaterally. Age-related metabolic decreases have also been reported for the insula, temporal poles, and lateral temporal cortices, the parietal lobes (including supramarginal, superior and inferior parietal cortices), the vicinity of ventricles, and in the frontobasal and perisylvian regions. Conversely, other regions appear unaffected during aging, including primary sensorimotor cortices, occipital cortices (particularly visual areas and posterior cingulate cortex), precuneus, mesial temporal lobes (hippocampus, amygdala and parahippocampal gyrus), thalamus, putamen, pallidum, and cerebellum [6].

Pathologic reductions in glucose metabolism indicate neuronal and synaptic loss, and are less commonly due to diaschisis and network efforts. Such changes can be seen in a variety of neurodegenerative conditions, as well as in epileptogenic lesions and the associated seizure networks.

IMAGING TECHNIQUE AND PROCESSING

The FDG brain PET imaging protocol is described in detail in published guidelines of the Society of Nuclear Medicine (SNM) and the European Association of Nuclear Medicine (EANM) [7,8]. Patients should fast for 4 to 6 hours prior to the study and avoid caffeine, alcohol, and drugs that affect cerebral glucose metabolism. In particular, sedatives, amphetamines, cocaine, narcotics, antipsychotic medications, and corticosteroids alter cerebral metabolism, generally by globally reducing FDG uptake in the brain. Patient activity and social interactions should be minimized (a quiet, dimly lit room) prior to, during, and up to 30 minutes following FDG injection, to avoid cerebral function and specific accumulations of tracer (e.g., language areas if the patient is talking to family members).

Blood glucose should be checked prior to FDG administration. If blood glucose is greater than 150–200 mg/dl, the patient should be rescheduled. In patients with diabetes, best images are achieved in a euglycemic situation during stable therapeutic management. FDG dose for adults is 185–740 MBq (5–20 mCi). Pediatric dose is 5.2–7.4 MBq/kg (0.14–0.20 mCi/ per kg), calculated by body weight. PET acquisition is typically started 50–60 minutes after FDG injection and lasts for 10–20 minutes. On a state-of-the-art PET with a high dose FDG (740 MBq, 20 mCi), imaging can be completed in 5 minutes.

Filtered back-projection and iterative methods are used for image reconstruction. Anatomic standardization of the PET image is performed by realigning the images in a standard stereotactic orientation using a standard brain atlas; or if acquired simultaneously, using co-registered computed tomography (CT) or MRI images. Both two- and three-dimensional acquisitions are then used to extract regional cortical metabolic activity. The FDG-PET images should be reconstructed and evaluated in trans-axial, coronal and sagittal planes. Vendor supported surface map reconstructions, a more recent technique for clinical practice, can be helpful for global assessment and diagnosis, but these have limitations and blind spots, so should not be the sole source of data for interpretation.

FDG-PET IN SUSPECTED DEMENTIA

Elderly individuals can present with memory impairment that is subjective (experienced by the patient but not detectable on a standardized exam) or objective (observable and documented on a clinical exam). Other common presenting symptoms noticed by the patients, their families, or friends include word-finding difficulty, repetitive statements or questions, poor concentration, getting lost in familiar surroundings, loss of interest in usual activities and personality changes. The most common dementias include Alzheimer's disease (AD, 60% to 80% of dementias), dementia with Lewy bodies (DLB, 10–30% of dementias), and frontotemporal lobar degeneration (FTLD, approximately 5% of all dementias, but the second most common diagnosis of dementia in individuals younger than 65 years of age) [9,10].

Underlying vascular disease is reported as a contributing factor in up to 45% of all patients with dementia, and may be the second most common primary cause of cognitive impairment in the elderly. Early evidence suggests that multifactorial interventions may have the potential to prevent or delay the onset of dementia [9]. Furthermore, recent anti-amyloid drug trials have actually been shown to delay the progression of AD [11], suggesting that clinicians may soon finally have effective medical therapies to treat dementia directly.

FDG-PET IS PARTICULARLY RECOMMENDED FOR SPECIFIC CLINICAL SUB-POPULATIONS, SUCH AS EARLY AND ATYPICAL CLINICAL PRESENTATIONS OF COGNITIVE IMPAIRMENT

The clinical assessment of dementia remains the mainstay of diagnosis and management; however, FDG-PET has come to play an increasingly important role. Recommendations from the European Federation of Neurological Societies (EFNS) include use of FDG-PET in patients in whom there is diagnostic uncertainty regarding the specific underlying cause of cognitive impairment or dementia [12], and brain FDG-PET is considered reasonable to help discriminate FTLD from AD in challenging cases. FDG uptake of the superficial and deep gray matter is assessed to identify focal or lobar-specific areas of decreased metabolism (sometimes unilateral or asymmetric) that can often be quite specific for certain common neurodegen-

erative conditions. Ultimately, accurate interpretation of FDG-PET in patients with dementia does not rest on the presence or absence of a single region of hypometabolism, but rather should take into account the pattern of hypometabolism across the cerebrum. For vascular cognitive impairment, brain FDG-PET is not highly specific, although hypometabolic regions can be identified that correlate with regions of white matter disease and remote infarcts on MRI. FDG-PET may, however, still be helpful in patients with suspected vascular cognitive impairment when a mixed dementia pattern is suspected. Note, FDG-PET has never reached widespread use for the imaging workup of patients with subcortical neurodegenerative processes such as Parkinson's disease (also called movement disorders).

FDG-PET FINDINGS IN ALZHEIMER'S DISEASE

Early characteristic features of AD include difficulty remembering recent conversations, names or events, apathy, and depression. Later features include impaired communication, disorientation, confusion, poor judgment, behavioral changes, as well as difficulty speaking, swallowing, and walking. Multiple FDG-PET studies have shown that individuals diagnosed with AD demonstrate a characteristic pattern of glucose hypometabolism, and the condition may be distinguished from healthy controls with 93–94% sensitivity and 93–99% specificity [13]. Indeed, an important, clinically useful finding is that a normal or essentially preserved cerebral FDG uptake pattern in patients with cognitive impairment makes AD less likely and suggests other causes of dementia or potentially reversible disorders such as depression.

Glucose metabolism in AD was demonstrated to be impaired in temporal-parietal association cortices, with the angular gyrus usually being located at the center of the metabolic impairment [14]. As dementia progresses, hypometabolism may extend to involve the frontal lobes, and the severity and extent of metabolic impairment in the temporal and parietal cortices increases [15] [Figure 1]. A key feature of AD is involvement of the posterior cingulate gyrus and the precuneus that are impaired at an early stage of the disease. Pronounced focal metabolic impairment may be detected in the occipito-temporo-parietal association areas in patients with posterior cortical atrophy syndrome (usually due to underlying AD pathology) [16]. AD metabolic impairment may be asymmetric or unilateral, where the most affected hemisphere is usually concordant with the predominant cognitive deficits, a finding that usually persists during progression. An important finding in AD patients (DLB and FTLD as well) is sparing of the basal ganglia, sensorimotor cortices (including the mesial occipital region – see below) and cerebellum. Early changes in cerebral metabolism were reported in patients with mild cognitive impairment. Meta-analyses of studies evaluating FDG-PET's ability to predict the conversion of mild cognitive impairment to AD demonstrate a sensitivity of 77–89% and a specificity of 74–85% [17], with higher accuracy relative to neuropsychological examination.

FDG-PET FINDINGS IN DEMENTIA WITH LEWY BODIES

DLB is clinically characterized by Parkinsonian-like extrapyramidal symptoms, sleep disturbances, fluctuating cognitive deficits and visual hallucinations. Patients also often have associated depression and agitation [18]. Unfortunately, DLB pathology can be co-morbid with AD pathology and some of the above symptoms occur in patients with exclusively underlying AD pathology, confounding diagnosis. Furthermore, DLB and

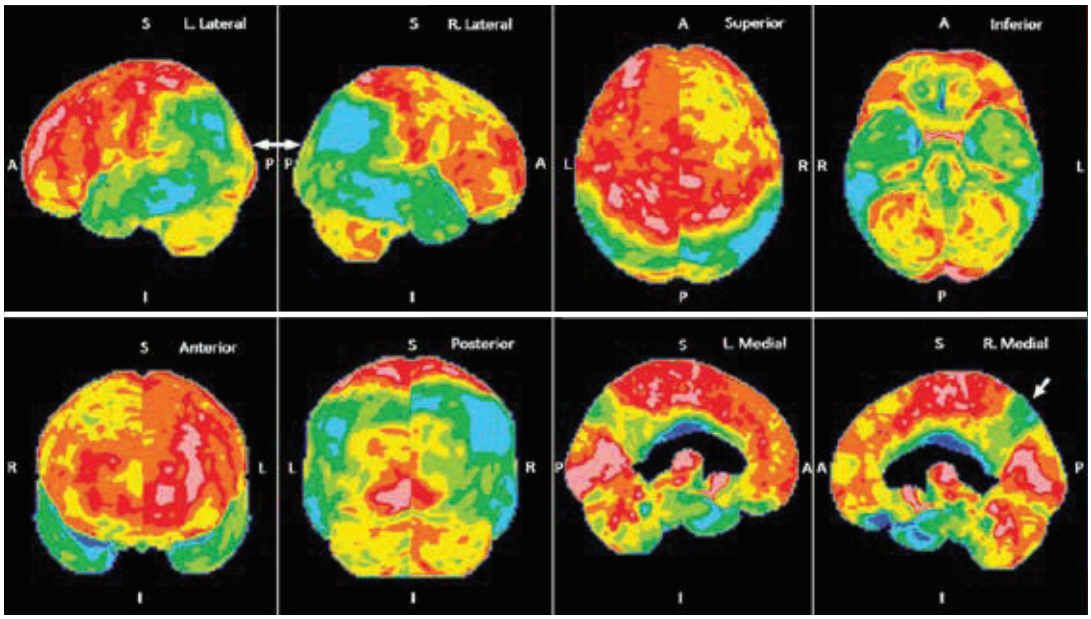


Figure 1. ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) 3-dimensional stereotactic surface projection maps of a 57-year-old man with early onset Alzheimer's disease as evidenced by severe lateral temporoparietal FDG hypometabolism, slightly asymmetric to the right (arrows, top left). Also noted is moderate FDG hypometabolism in the precuneus (arrow, bottom right). There is relative preservation of FDG uptake in the sensorimotor region and mesial occipital cortices (a 10-band color scale is set with red to be normal cortical FDG uptake)

Parkinson's disease share underlying histopathological changes (such as intraneuronal aggregates of α-synuclein in Lewy bodies and Lewy neurites [19]). The α-synuclein distribution in Parkinson's disease is more focal initially and follows a topographic specific spread, where as in DLB the pathology is more widespread early and associated with much earlier cognitive impairment. In FDG-PET, DLB findings significantly overlap with those of AD, including bilateral parietal and posterior temporal cortex hypometabolism [20]. In some patients, one can observe characteristic lateral and medial occipital cortex hypometabolism [Figure 2], likely related to impairment of visual perception, as well as relative preservation of the posterior cingulate cortex to differentiate DLB patients from AD patients. Importantly, if the occipital cortex does not demonstrate hypometabolism, DLB and AD cannot reliably be distinguished with FDG-PET– this is unfortunately a limitation of FDG-PET for excluding DLB. Not all DLB patients have visual hallucinations at presentation and these patients are more likely to have normal-appearing mesial occipital cortex FDG metabolism [21].

FDG-PET IS AN IMPORTANT TOOL FOR PRE-SURGICAL LOCALIZATION AND LATERALIZATION OF EPILEPTOGENIC FOCI IN EPILEPSY PATIENTS WITH NORMAL OR DISCORDANT MAGNETIC RESONANCE IMAGING

FDG-PET FINDINGS IN FRONTOTEMPORAL LOBAR DEGENERATION

FTLD entails a set of genetically heterogeneous and sometimes overlapping clinical disorders with complex classification [22]. The most common subtype, called behavioral variant FTD (bvFTD, also known as Pick's disease), is characterized by prominent early changes in personality, interpersonal relationships, and conduct. The second subtype of FTLD, primary progressive aphasia (PPA), affects language skills, speaking, writing, and comprehension. It is comprised of three variants: progressive nonfluent/agrammatic variant (agPPA), logopenic variant (lvPPA), and semantic variant (svPPA). AgPPA is characterized by impairment in speech production and grammar with a telegraphic pattern of speech. In contrast, svPPA is a fluent aphasia with loss of word meaning and conceptual knowledge. lvPPA is most commonly associated with AD (making it a PPA variant but not an FTLD), with presenting deficits in word-search and repeating complex sentences. Patients with PPA who are not identified early or who are assessed later in the course of disease may have memory problems and impairment in other cognitive domains with more global FDG hypometabolism. These symptoms make it difficult to distinguish later stage PPA from AD or bvFTD since the key discriminating feature is that in PPA, language impairment precedes impairment in other cognitive domains by 1 to 2 years.

FTLD most commonly demonstrates frontal and/or anterior temporal predominant hypometabolism on FDG-PET [23] with sparing of the parietal cortex. These findings have a high diagnostic accuracy (~90%) for discriminating FTLD from AD, especially early in the course of the disease. Specific patterns of metabolic impairment have been associated with different subtypes of FTLD, although there is considerable overlap of metabolic deficits (and clinical features) especially as disease progresses. BvFTD patients show hypometabolism of frontal lobe regions on FDG-PET, specifically involving orbitofrontal, frontopolar, medial frontal, dorsolateral, and lateral inferior frontal regions as well as anterior cingulate cortices [24] [Figure 3].

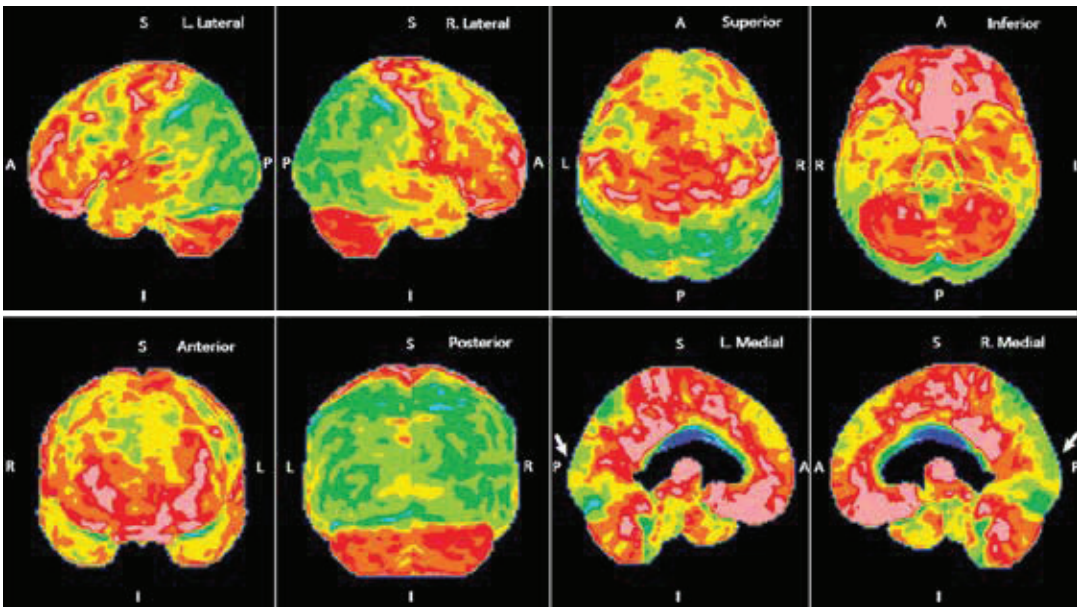


Figure 2. ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) 3-dimensional stereotactic surface projection maps of an 82-year-old woman who presented with fluctuating mental status, Parkinsonism, and vivid hallucinations of strangers in her kitchen. The patient has moderate to severe lateral parietal and occipital hypometabolism that involves the occipital poles and mesial cortex (arrows, bottom right). The mesial occipital FDG hypometabolism supports further clinical evaluation for underlying DLB pathology

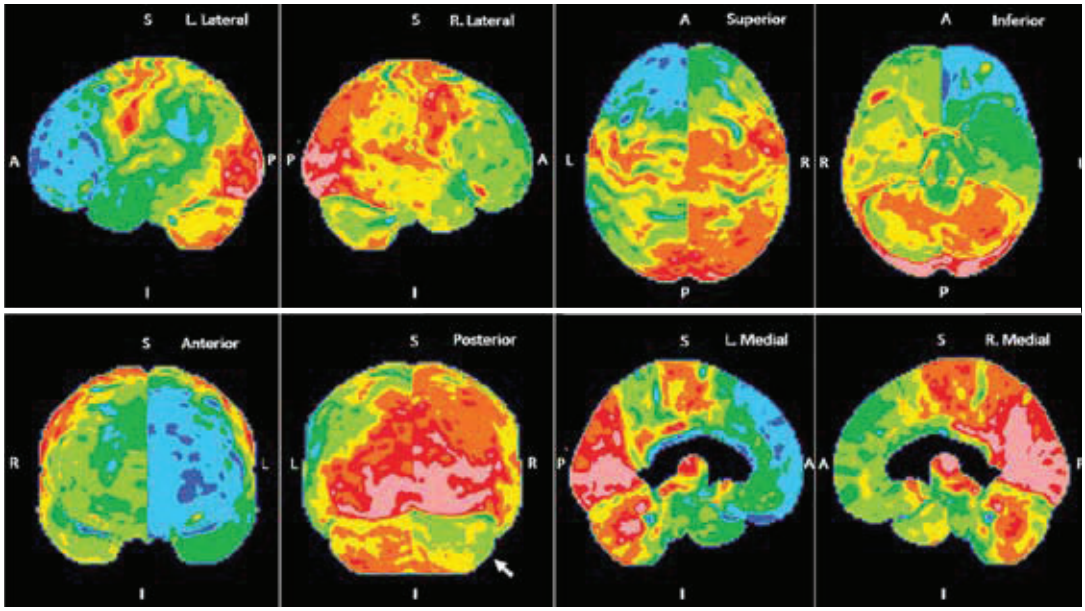


Figure 3. ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) 3-dimensional stereotactic surface projection maps of an 86-year-old woman with frontotemporal dementia (behavioral variant) as evidenced by severe left frontal hypometabolism, moderate lateral left temporoparietal hypometabolism, and mild right lateral temporal, frontal and parietal hypometabolism. Note that FDG metabolism (in red) for the precuneus, mesial occipital, and primary motor cortices is normal. In our experience striking left-right asymmetries in FDG metabolism are more common in FTLD dementias. There also is right cerebellar diaschisis (arrow)

Metabolic impairments spread to the temporal cortex and subcortical regions in more advanced stages of bvFTD [23]. Patients with svFTD typically show severe metabolic impairment of the anterior parts of the left temporal lobe, often also extending into basolateral parts of the frontal lobe, as well as caudate nucleus, insula, and hippocampus [25]. The key metabolic deficits in progressive non-fluent aphasia are typically asymmetrically situated in the productive language areas of the left hemisphere, including inferior and middle frontal, dorsolateral prefrontal and frontopolar cortices, and middle and inferior temporal regions.

FUTURE PERSPECTIVES FOR PET IN DEMENTIA

The recent development of amyloid-specific [^{18}F] derivative PET ligands has enabled in vivo visualization of fibrillar amyloid-beta (Aβ) plaques [26]. However, since brain amyloidosis is a necessary but not sufficient condition for diagnosis of AD, the diagnostic value of amyloid PET is more exclusionary than inclusionary, and the Medicare and U.S. National Institutes of Health-funded Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study is re-examining its cost-effectiveness within the U.S. healthcare system [27]. Both amyloid-positive and amyloid-negative results may affect diagnosis and treatment in patients with and without dementia [28]. Emerging literature of next generation radiotracers for assessing cerebral tau protein burden may eventually supersede amyloid and FDG-PET radiotracers for the clinical evaluation of dementia, particular regarding diagnostic specificity. The introduction of tau-PET techniques is reshaping the AD research field, enabling a more targeted evaluation of the original amyloid cascade hypothesis, which remains highly controversial. A detailed discussion of these issues is beyond the scope of this review, but can be found in recent review articles [29].

FDG-PET FINDINGS IN EPILEPSY

Epilepsy is a common chronic neurological disorder characterized by seizures as a result of abnormal coherent neuronal activity in the brain [30]. Approximately 65 million people worldwide have epilepsy. Seizures are controlled with medical therapy in approximately 70% of patients. However, nearly one-third of patients with epilepsy become medically intractable and may benefit from surgical resection of the epileptogenic brain lesion [31]. In selected patients with focal structural lesions, surgery renders up to 60-90% of those with unilateral temporal lobe epilepsy (TLE) [32] seizure free, and up to 70% of those with a focal cortical malformation seizure free [33].

Surgery can substantially improve the long-term outcomes of seizure control in individual patients. When the results of video EEG, MRI, and clinical status are discordant, or no morphological abnormalities are detected on MRI, interictal FDG-PET may play a key role in the lateralization or localization of the epileptic region and in guidance for subsequent subdural electrode placement in patients with intractable partial epilepsy [34]. FDG-PET scanning may provide additional diagnostic support for a suspected epileptogenic focus identified on MR imaging, or may provide independent information regarding a potential epileptogenic focus in the setting of either a normal MR image or an MR image with multiple structural abnormalities. FDG-PET has proven to be the most sensitive imaging technique for presurgical localization of epileptogenic foci, of which the expected image pattern is hypometabolism [Figure 4]. The reported sensitivity of FDG-PET in detecting an epileptogenic

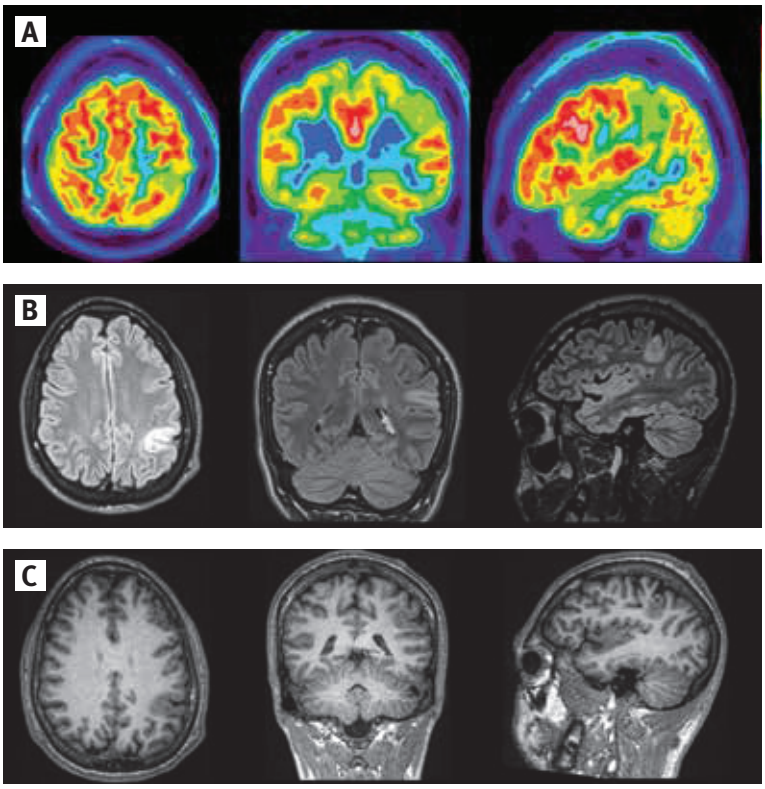
brain region is 85–90% in TLE, but lower (45–60%) in extra-temporal epilepsy, depending on the localization of the focus [34]. Recent findings suggest that FDG-PET is reliable for localizing type 2 focal cortical dysplasia (FCD) [35]. Interictal FDG-PET was able to lateralize the seizure focus in 95% of MRI positive, 69% of MRI equivocal, and 84% of MRI negative TLE patients [36]. FDG-PET contributed to decision making in 53% of pre-surgical patients with normal or discordant MRI [37]. However, interictal FDG-PET cannot precisely define the surgical margins. The area of hypometabolism may extend beyond epileptic zones [34], which makes precise localization of the epileptogenic lesion difficult. Studies of patients with TLE have demonstrated that greater severity of preoperative extra-temporal, and bilateral hypometabolism was associated with a poor seizure outcome after surgery [38]. However, ipsilateral PET hypometabolism showed a predictive value of 86% for good outcome [39]. Notably, recent seizure activity may cause a complex pattern of increased and decreased metabolism, depending on the time between FDG injection and most recent seizure. Ideally, continuous EEG monitoring during the FDG uptake period and reliable patient or caretaker history for recent seizures are important for an optimal FDG-PET brain study. In our clinic, we try to reschedule any epilepsy patient for FDG PET who reports a seizure within 48 hours of the scheduled imaging study.

Although FDG remains the dominant PET radiotracer used in clinical practice, over the last decade several PET tracers for pre-surgical evaluation of patients with epilepsy have also been studied to better understand in vivo neurochemistry of the epileptic brain. These include specific tracers for neurotransmitter and neuromodulator systems, including the GABA, serotonin, dopamine, glutamate, acetylcholine, adenosine, and opioid systems. However, practical limitations of using these radiotracers include the lack of commercially available radiotracers, a short half-life that necessitates an onsite cyclotron, a moderate signal-to-noise ratio, and the need for arterial blood sampling to model tracer-binding features. These issues are beyond the scope of the current report, but for interested readers, please see a suggested review article [40].

CONCLUSIONS

FDG-PET neuroimaging provides a wide array of functional and metabolic information that may elucidate mechanisms of neurologic diseases and guide therapeutic approaches. A large body of literature has demonstrated that FDG-PET substantially improves diagnostic accuracy and differential diagnosis of several neurodegenerative diseases, and enables earlier and better treatment planning. For epilepsy, FDG-PET remains can provide a key component of presurgical localization of the epileptogenic lesion or zone, and can potentially help in the setting of diagnostic uncertainties.

Figure 4. Co-registered axial, coronal and sagittal ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) **[A]**, FLAIR **[B]**, and T1-weighted images **[C]**, of a 30-year-old man with focal cortical dysplasia in the left inferior parietal lobule, as evidenced by a slightly expansile cortical **[B,C]**, lesion with associated FDG hypometabolism **[A]**, surgical pathology confirmed a type 2 focal cortical dysplasia



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"If I could I would always work in silence and obscurity, and let my efforts be known by their results"

Emily Jane Brontë (1818–1848), English novelist and poet who is best known for her only novel, *Wuthering Heights*, considered a classic of English literature

"The idealists and visionaries, foolish enough to throw caution to the winds and express their ardor and faith in some supreme deed, have advanced mankind and have enriched the world"

Emma Goldman (1869–1940), anarchist political activist and writer