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Brain: Normal Variations and Benign Findings in FDG PET/CT imaging

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SYNOPSIS

Brain 18F-FDG PET allows the in vivo study of cerebral glucose metabolism, reflecting neuronal and synaptic activity.

18F-FDG PET has been extensively used to detect metabolic alterations in several neurological diseases vs. normal aging. However, healthy subjects exhibit variants of 18F-FDG distribution, especially as associated with aging. 18F-FDG uptake is usually homogeneous and symmetrical, but areas of slightly higher activity are observed in basal ganglia, frontal eye fields, posterior cingulate cortex and visual cortex. On the contrary, relatively lower metabolic activity is observed in medial temporal cortex.

This review will focus on 18F-FDG PET findings in so-called normal brain aging, and in particular on metabolic differences occurring with aging and as a function of people's gender. The effect of different substances, medications and therapy procedures will be discussed, as well as common artifacts.

Keywords

18F-FDG PET; normal brain; normal variants; aging brain

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INTRODUCTION

Glucose is the main metabolic substrate of the brain and its oxidation produces the amount of energy that is necessary for an adequate cerebral activity.

The positron emission tomography (PET) tracer 18F-fluorodeoxyglucose (18F-FDG) allows the in vivo study of glucose metabolism, and since its introduction in 1976, it is the most widely used PET tracer in both clinical and research settings ¹.

The local glucose consumption, and thus 18F-FDG cerebral uptake, correlates strictly with local neuronal activity, and proportionally increases with stimulus intensity or frequency ² or decreases in conditions of sensory deprivation ³. Such metabolic variations take place at the level of synaptic connections ⁴. As such, neurotransmission and signal transduction are the processes with the highest energetic requirements. It has been estimated that the energetic demand of neurotransmission and related events exceeds 80% of total cerebral energetic consumption ⁵.

Connections between neurons are carried out mainly by excitatory glutamatergic synapses, which account for the great majority of all cortical synapses, yielding an energetic consumption of around 80% of total cortical consumption ⁵.

A large body of literature demonstrated that 18F-FDG PET adds value to diagnostic evaluation of several neurological diseases. In particular, 18F-FDG PET substantially improves diagnostic accuracy and differential diagnosis, and enables earlier and better treatment planning of neurodegenerative disorders^{6,7}.

While the majority of studies have focused on detection of abnormal, disease-specific 18F-FDG distribution patterns, relatively little is known about brain glucose metabolism in clinically and cognitively normal, healthy individuals, and about “normal variants” of FDG uptake in this population.

Thorough knowledge of the normal variants of brain function, occurring in healthy aging or related to gender, is critical for detection of abnormal findings and for investigating neurological diseases.

This review will focus on 18F-FDG PET findings in so-called normal brain aging, and in particular on metabolic differences occurring with aging and as a function of people’s gender. The effect of different substances, medications and therapy procedures will be discussed, as well as common artifacts.

IMAGING TECHNIQUE

Updated procedure guidelines for 18F-FDG PET brain imaging have been published by the Society of Nuclear Medicine in 2009 ⁸ and include: all relevant information to be collected during the procedure, instructions for patient’s management and preparation for PET scanning, and a summary of the standardized acquisition protocol. These are summarized in Box 1, 2 and 3, respectively.

Box 1**Relevant patient history and data**

Focused history: head trauma, known neurological or psychiatric disorders, brain tumors, prior brain operations
Clinical history: patient complaints, neurological/psychiatric examination, mental status exam (mini-mental state examination, neuropsychological tests), cognitive impairment
Recent morphologic imaging studies (e.g. computed tomography, magnetic resonance imaging or prior PET or single photon computed tomography brain studies)
Current medications

Box 2**Patient preparation before PET scanning**

Fasting for at least 4–6 hours
Oral hydration with water should be encouraged
Avoid caffeine, alcohol, or drugs that may affect cerebral glucose metabolism
Check blood glucose level (ideally not greater than 150–200 mg/dL)
Environmental conditions: “resting state”, patient with eyes open and ears unoccluded in a quiet, dimly-lit room, with minimal background noise
Start intravenous line for 18F-FDG administration (at least 10 minutes prior to tracer injection)

Box 3**Acquisition protocol**

Administered dose	185–370 MBq
Acquisition starting time	30 minutes post-injection 60 minutes post-injection (oncology)
During acquisition	Well-tolerated head immobilization procedures should be implemented, to minimize head movements
Acquisition duration	20 minutes (depending on PET equipment and patient compliance)
Reconstruction	Transaxial matrix size: 128 × 128 or 256 × 256 Typical pixel size: 2–4 mm

18F-FDG PET images should be reconstructed in transaxial, coronal and sagittal planes.

For a comprehensive evaluation of brain 18F-FDG PET images, all three projection planes should be used. The transaxial plane is recommended for evaluation of all cortical and subcortical structures. Transaxial images should be reoriented both along anterior commissure-posterior commissure (AC-PC) line and temporal long axis (for better assessment of temporal lobe) (Figure 1). The coronal plane is recommended for inspection of posterior cingulate, angular gyri, and medial temporal lobes (including hippocampal areas). The sagittal plane is valuable in evaluations of the frontal and temporal poles.

NORMAL ANATOMY

Glucose is the only source of energy of the brain, which is known to account for as much as 20% of total-body glucose metabolism in the fasting state. For these reasons, brain exhibits an intense 18F-FDG uptake, with higher activity in the grey matter as compared to the white matter.

In resting conditions, cerebral metabolic rate values for glucose are approximately 15 micromol/min/100g for the white matter, and 40–60 micromol/min/100g for the grey matter. In the normal brain, the grey to white matter activity ratio is 2.5 to 4.1.

Differences of 18F-FDG distribution have been observed among different brain regions. 18F-FDG uptake is usually higher in the frontal, parietal and occipital areas than in temporal cortex, and the basal ganglia have slightly higher activity than the cortex⁹. Moreover, focal areas of increased uptake were observed in frontal eye fields, posterior cingulate cortex and visual cortex of normal subjects. Metabolic activity is lower in medial temporal cortex, including hippocampal areas, than in neocortical regions (Box 4 and Figure 2)^{9,10}.

Box 4	
Normal pattern of uptake	
Areas of higher uptake	<ul style="list-style-type: none"> • Basal ganglia • Frontal eye fields • Posterior cingulate cortex • Visual cortex
Areas of lower metabolic activity	<ul style="list-style-type: none"> • Medial temporal cortex

Brain 18F-FDG uptake is usually homogeneous and symmetrical. Slight asymmetries in 18F-FDG uptake have been observed in the Wernicke area, the frontal eye fields and the angular gyrus, with a prevalence of generally less than 10%.¹¹.

IMAGING FINDINGS

Several 18F-FDG PET studies investigated the normal variants of brain metabolic activity. Subtle differences in cerebral metabolic activity have been observed among cognitively normal, healthy individuals, mostly as related to the effects of scanning time, age and gender, but also to the effect of medications and therapy procedures.

Scanning time

Regional 18F-FDG uptake differences were observed in the normal human brain depending on scanning starting time after intravenous tracer injection.

Some studies compared 18F-FDG images obtained at 60 minutes post injection (p.i.) to earlier time frames (30 minutes p.i.) in the same individuals, and showed relatively higher 18F-FDG uptake in bilateral posterior cingulate gyrus, parietal and frontal association cortices, and subcallosal cortices, and relatively lower uptake in cerebellum and orbito-frontal areas in 60 minutes p.i. scans as compared to earlier images)¹². While the cause of such effects remains unclear, this might be due to regional differences in 18F-FDG transportation from plasma to tissue, or in glucose phosphorylation or dephosphorylation kinetics in different regions over time¹³.

Age

Since its early phases of development, the human brain experiences several structural and functional changes.

According to the few 18F-FDG PET studies on brain maturation in children, global cerebral metabolic rate of glucose is low in the newborn period (13–25 micromol/min/100g), and rapidly rises to adult normal values (19–33 micromol/min/100g) at 2 years of age¹⁴. Global cerebral metabolic activity continues to rise to values of 49–65 micromol/min/100g by age 3–4 years, and remains stable until approximately 9 years, when it begins to decline, reaching characteristic adult values by the end of the second decade of life¹⁴. This time-course of global cerebral metabolic rate of glucose during childhood has been matched to the process of initial overproduction and subsequent elimination of excessive neurons and synapses occurring in the developing brain.

In addition to changes in global cerebral metabolic activity, normal brain development is associated to changes in metabolic patterns. In neonates, local cerebral glucose metabolism is highest in primitive areas, such as brainstem, cerebellar vermis, thalamus and primary sensorimotor cortex^{14,15}. Glucose metabolism in parietal, temporal (including mesial temporal region), occipital cortices and basal ganglia increases at 3–5 months of age^{14,15}.

Finally, the frontal cortex becomes metabolically active between 6 and 8 months^{14,15}.

While the window into brain metabolic changes in childhood is mainly derived from a few studies, more numerous 18F-FDG PET studies examined the effect of age on normal adult cerebral metabolic rate of glucose.

During aging, the brain undergoes both structural and functional changes, whose regional distribution mirrors the reported cognitive decline usually observed in the normal elderly population¹⁶.

Enlargement of the ventricles and cortical sulci, due to brain atrophic alterations, is one of the major changes that may occur in middle aged to old healthy individuals. This age-related enlargement of cerebrospinal fluid spaces is reflected in brain metabolic reduction in the vicinity of ventricles, in frontobasal and perisylvian structures on 18F-FDG PET¹⁷. Since these structures are mostly surrounded by white matter, their age-related hypometabolism is most likely due to white matter atrophy occurring in healthy aging.

Besides white matter changes, healthy aging is associated with grey matter alterations.

Global cerebral metabolic rates of glucose inversely correlate with age, with a reported decline of 12–13% between ages 20 and >70 years^{18–20}.

In addition to the global decrease in brain metabolism, a number of studies have reported specific patterns of age-related regional metabolic declines.

The most common metabolic reductions with advancing age have been observed in the frontal lobes (Figure 3). In particular, the reduction of 18F-FDG uptake involves anterior cingulate cortex, dorsolateral and medial prefrontal cortices, and orbitofrontal cortex, bilaterally^{17,19–28}. The metabolic reduction in medial prefrontal cortices is correlated with age-associated cognitive decline in healthy subjects²⁸.

Age-related metabolic decreases have also been observed in neocortical regions other than frontal cortex, such as the insula^{20,24}, the temporal lobes (particularly the temporal pole and lateral temporal cortex)^{19,22,24} and the parietal lobes (including supramarginal, superior and inferior parietal cortices)^{19,20,24}.

In contrast, several cortical and subcortical areas have been reported to be relatively unaffected during aging, including primary motor cortices, occipital cortices (particularly visual areas and posterior cingulate cortex), precuneus, mesial temporal lobes (hippocampus, amygdala and parahippocampal gyrus), thalamus, putamen, pallidum and cerebellum^{17,19,20,24,27,29}. Age-related metabolic changes in healthy individuals are summarized in Box 5.

Box 5

Age-related metabolic changes in healthy individuals

Age-related hypometabolism

Frontal lobes

- anterior cingulate cortex
- dorsolateral and medial prefrontal cortices
- orbitofrontal cortex

Insula

Temporal lobes

- temporal pole
- lateral temporal cortex

Parietal lobes

- supramarginal, superior and inferior parietal cortices

Least altered regions during aging

Primary motor cortices

Occipital cortices

- visual areas
- posterior cingulate cortex

Precuneus
Mesial temporal lobes
• hippocampus
• amygdala
• parahippocampal gyrus
Thalamus
Putamen, pallidum
Cerebellum

Brain metabolic changes observed in normal aging support the developmental theory, according to which age-related brain changes follow the phylogenetic and ontogenetic axes³⁰. The topographic pattern of metabolic decline in normal aging matches in a reverse sense the metabolic functional changes observed in developing human brain. The first structures to neurally develop are the same areas that are spared from metabolic deterioration occurring with age (i.e., brainstem, thalamus, cerebellum, sensorimotor cortex, hippocampus), whereas the frontal regions, which become metabolically active during the third and last levels of development of the central nervous system, are the most consistently affected by the aging process.

The regional distribution of age-related hypometabolism, which involves primarily the frontal lobes, is substantially different from the patterns of brain metabolic impairment typical of Alzheimer's disease (AD) and other dementias. AD is characterized by hypometabolism in precuneus and posterior cingulate cortex, parieto-temporal regions and more variably, medial temporal regions, while the frontal cortex becomes affected at late disease stages^{6,31}. As many aging individuals experience memory loss, such metabolic differences make 18F-FDG PET particularly useful in the diagnosis of AD vs. normal aging, and in the understanding of age-related vs. AD-related memory impairment. While memory impairment due to AD is strictly linked to posterior cingulate and hippocampal hypometabolism, memory deficits observed during normal aging may reflect mainly a failure of encoding and retrieval processes of episodic memory, which depends on frontal cortex integrity³².

The identification of brain metabolic abnormalities typical of AD in 18F-FDG PET of cognitively normal subjects has a strong predictive value for future development of AD. Longitudinal 18F-FDG PET studies in normal individuals who later declined to AD demonstrated that AD-related metabolic reductions precede the onset of clinical symptoms by many years and correlate with diagnosis of AD³³. Hippocampal metabolic impairment usually precedes that in the cortical regions in cognitively normal individuals declining to dementia due to AD, while the cortical hypometabolism becomes evident later³³.

Gender

Several 18F-FDG PET studies focused on the effect of gender on brain metabolism to highlight possible metabolic differences and corresponding behavioral differences between men and women.

Brain volume is reportedly greater in men than women, with a higher percentage of grey matter in female and a higher percentage of white matter in male subjects³⁴. However, 18F-FDG findings have been controversial, as summarized in Table 1.

The inconsistencies among studies are likely due to differences in sample size, subjects' age, and image analysis procedures. Hormones (i.e. estrogen) are another potential source of variation on cerebral metabolism of female subjects³⁵. Correction, or lack of, for differences in brain size and skull thickness between gender groups is another potential confounding factor which should be taken into account³⁶.

Substances/Medications

Several substances and medications may influence the cerebral metabolic rate of glucose, predominantly altering global metabolism but also with possible effects on regional distribution (Box 6).

Box 6

Effects of several substances and medications on cerebral glucose metabolism in normal individuals

Substance/Medication	Effect on brain glucose metabolism
Caffeine	Global mean reduction (–18%), most prominent in anterior cingulate cortex
Alcohol	Global mean reduction (from –9% to –25%), most prominent in occipital cortex and cerebellum
Amphetamines	Low-doses: metabolic decrease in cortical and subcortical areas High-doses: global metabolic increase, in particular in caudate nucleus, thalamus and anterior cingulate cortex Long-term effect: metabolic reduction in cingulate cortex, striata, amygdala and hippocampus
Cocaine	Acute: increased metabolic activity in medial prefrontal cortex, expanding in prefrontal, sensorimotor, anterior cingulate cortices and in striata Long-term: reduced metabolic activity in striata and orbito-frontal cortex
Anaesthetics	Global mean reduction (–46%)
Benzodiazepines	Global metabolic reduction, most prominent in occipito-cerebellar regions
Neuroleptics	Metabolic increase in striata and thalamus Metabolic decrease in frontal and anterior cingulate cortices
Corticosteroids	Generalized reduction of glucose metabolic activity
Chemotherapy	Reduction in cortical metabolic activity (–17%) Metabolic decrease in inferior frontal cortex

Data from Refs 44–62.

Among the substances capable of altering cerebral metabolism, caffeine is one of the most commonly used. Caffeine is part of the methylxantine family and plays a vasoconstrictive effect. It has been shown that caffeine assumption prior PET examination decreases global cerebral glucose metabolism as measured with 18F-FDG with a mean change of –18%; the reduction is particularly prominent in the anterior cingulate cortex⁴⁴.

Alcohol has a broad range of actions on many neurotransmitter systems. The brain metabolic response to acute administration of ethanol in healthy subjects has been

investigated in several studies, and it has been consistently shown a global reduction of brain glucose metabolism after ethanol administration, although with various degrees across different studies (from -9% to -25%)⁴⁵⁻⁴⁷. Discrepancies in the amount of metabolic reduction could be due to differences in: amount of ethanol administered, PET scanners, composition of sample and data analyses. The greatest metabolic decrease in absolute metabolism usually occurs in the occipital cortex and in cerebellum. Moderate hypometabolism has been observed in the limbic system, parietal cortex, frontal cortex, cingulate gyrus, temporal cortex, thalamus and midbrain. The smallest decrease could be observed in the basal ganglia⁴⁵⁻⁴⁷.

Abuse substances such as amphetamines and cocaine significantly alter glucose brain metabolism. Low doses of amphetamines affect cerebral metabolism by decreasing metabolic rates of glucose of cortical and subcortical areas⁴⁸. On the contrary, at high doses amphetamines increase whole-brain glucose metabolism, particularly in striata, thalami and anterior cingulate cortex⁴⁹. Amphetamine abuse exerts also long-term effects on the brain: 18F-FDG PET of ecstasy abusers, even after detoxification, demonstrates hypometabolism in striata, amygdala, hippocampus and cingulate cortex⁵⁰.

Cocaine assumption before 18F-FDG PET examination induces a significant increase of brain metabolism in several cortical and subcortical areas, directly related to the substance exposure⁵¹. Cocaine-induced increases in brain metabolism are localized in the medial prefrontal cortex in cases of limited exposure. As cocaine exposure increases, hypermetabolism could be observed in the prefrontal and anterior cingulate cortices and in regions of sensorimotor processing. Enhanced metabolic activity may be also found in the striatum⁵¹. Besides, 18F-FDG PET scans of detoxified cocaine abusers may show alterations of glucose brain metabolism, with significant reduction of metabolic activity in striata and orbito-frontal cortex⁵².

Among the medications that have been shown to alter brain glucose metabolism, there are several drugs acting on the central nervous system, such as anaesthetics, sedatives and neuroleptics, as well as corticosteroids and chemotherapy agents.

Anaesthetics, as propofol, isoflurane and barbiturates, produce a global, substantially uniform, metabolic reduction, at levels reaching -46% of normal metabolic activity^{53,54}.

Benzodiazepines as lorazepam induce a significant decrease in global cerebral metabolism,, with more prominent reduction in occipital cortex and cerebellum⁵⁵.

Neuroleptic drugs as haloperidol have been demonstrated to increase metabolic activity in striata and thalami and to reduce glucose metabolism in frontal lobes and anterior cingulate cortex⁵⁶.

Moreover, consumption of corticosteroids before 18F-FDG PET scan induces alterations of cerebral metabolism, with a generalized reduction of glucose metabolic activity⁵⁷.

Finally, brain 18F-FDG PET scan in cognitively normal subjects may show a lower brain metabolism (at levels around -17%) after chemotherapy than before the treatment⁵⁸. This

condition, known as “chemo-brain”, could be observed also years after the chemotherapy, with reduction of cortical metabolism, particularly in inferior frontal gyrus^{59,60}.

Therapy procedures

Changes occurring after radiotherapy, especially external beam radiotherapy, may mimic hypometabolism due to neurodegeneration.

In the first weeks immediately after radiotherapy, radiation may induce elevated 18F-FDG uptake in normal brain tissues, due to inflammatory changes^{63,64}. These post-therapy changes could be visible also in the epithelial surfaces.

A long-term consequence after radiotherapy may be a reduction up to –5% of cerebral metabolic activity in the irradiated brain tissue, as compared to non-irradiated brain tissue⁶⁵.

ARTIFACTS

The main factors that could cause artifacts on 18F-FDG PET images, potentially leading to interpretation pitfalls, are the following:

- *Hyperglycemia.* As 18F-FDG enters and is metabolized in cells using the same mechanisms as glucose, elevated plasma glucose levels result in decreased uptake of 18F-FDG in the normal brain tissue⁶⁶. In particular, hyperglycemia could induce a reduction of 18F-FDG uptake in all brain regions (including cortical and subcortical gray matter, white matter and cerebellum), at levels reaching –54%⁶⁷.
- *Patient motion.* Patient motion during PET scanning introduces errors in the attenuation correction and image blurring leading to artifactual changes in activity concentrations and degradation of image resolution. It has been demonstrated that a mismatch as little as 5 mm may cause an error as much as 10% in measured 18F-FDG PET activity, and a 10-mm mismatch can cause a 25% error^{68,69}. Lateral movements of patient’s head during image acquisition cause a common motion artifact showing unilateral cerebral hypometabolism, involving also the ipsilateral scalp. In these cases, non attenuation corrected PET images should be observed, demonstrating the displacement of patient’s head. These artifacts could be corrected using computer realignment or calculating the attenuation correction with a standard attenuation coefficient.
- *Calculated attenuation.* When a transmission image or a computed tomography (CT) scan is not available, attenuation correction could be calculated using a standard attenuation coefficient. However, this method does not take into account differences across subjects, in particular variations of skull thickness. For example, subjects with hyperostosis frontalis may show artifactual reduction of frontal metabolic activity.
- *Metallic artifacts.* CT-based correction method overestimates the attenuation of metallic objects included in the field of view and results in artifactually increased 18F-FDG activity in PET images. When metallic artifacts are suspected, the

absence of high activity in uncorrected images should be confirmed, in order to prevent potential misinterpretation.

SUMMARY

Brain 18F-FDG PET allows the in vivo study of cerebral glucose metabolism, reflecting neuronal and synaptic activity.

18F-FDG PET has been extensively used to detect metabolic alterations in several neurological diseases vs. normal aging. However, healthy subjects exhibit variants of 18F-FDG distribution, especially as associated with aging.

In normal healthy subjects, cerebral metabolic rate values for glucose are around 15 micromol/min/100g for the white matter, and around 40–60 micromol/min/100g for the grey matter. 18F-FDG uptake is usually homogeneous and symmetrical, but areas of slightly higher activity are observed in basal ganglia, frontal eye fields, posterior cingulate cortex and visual cortex. On the contrary, relatively lower metabolic activity is observed in medial temporal cortex.

During aging, global cerebral metabolic rate of glucose decreases with a reported decline of 12–13% between ages 20 and >70 years. Healthy aging is associated with mild cortical hypometabolism involving preferentially the frontal lobes, in particular anterior cingulate cortex, dorsolateral and medial prefrontal cortices, and orbitofrontal cortex.

Age-related metabolic reductions are also observed in the insula, the temporal lobes (particularly the temporal pole and lateral temporal cortex) and the parietal lobes.

primary motor cortices, occipital cortices (particularly visual areas and posterior cingulate cortex), precuneus, mesial temporal lobes (hippocampus, amygdala and parahippocampal gyrus), thalamus, putamen, pallidum and cerebellum are the least age-affected regions.

Gender-related differences have been reported although definitive results remain to be established.

18F-FDG uptake in the normal brain could be affected by several substances and medications including caffeine, alcohol, abuse drugs as amphetamines and cocaine, sedatives, neuroleptics, corticosteroids and chemotherapy agents. Besides, radiotherapy could have both short-term and long-term effects on brain metabolism, causing 18F-FDG uptake changes in irradiated brain tissue.

Finally, several artifacts may influence 18F-FDG brain distribution and cause interpretation pitfalls.

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Key Points

- Brain 18F-FDG PET allows the in vivo study of cerebral glucose metabolism, reflecting neuronal and synaptic activity.
- 18F-FDG PET has been extensively used to detect metabolic alterations in several neurological diseases vs. normal aging; however, healthy subjects exhibit variants of 18F-FDG distribution, especially as associated with aging.
- Healthy aging is associated with mild cortical hypometabolism involving preferentially the frontal lobes, in particular anterior cingulate cortex, dorsolateral and medial prefrontal cortices, and orbitofrontal cortex.
- 18F-FDG uptake in the normal brain could be affected by several substances and medications including caffeine, alcohol, abuse drugs as amphetamines and cocaine, sedatives, neuroleptics, corticosteroids and chemotherapy agents.
- Several artifacts may influence 18F-FDG brain distribution and cause interpretation pitfalls.

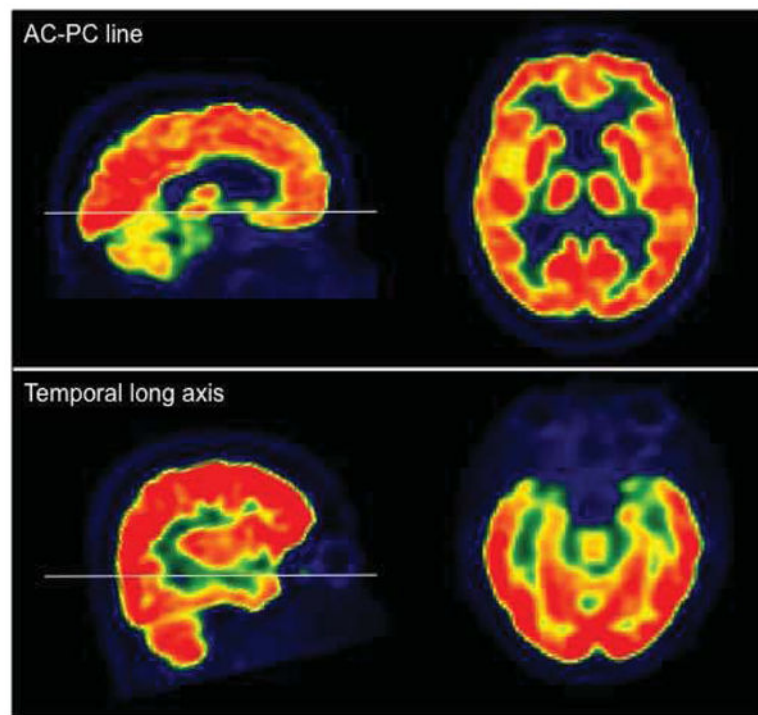


Figure 1.
18F-FDG PET images oriented along AC-PC line and temporal long axis.

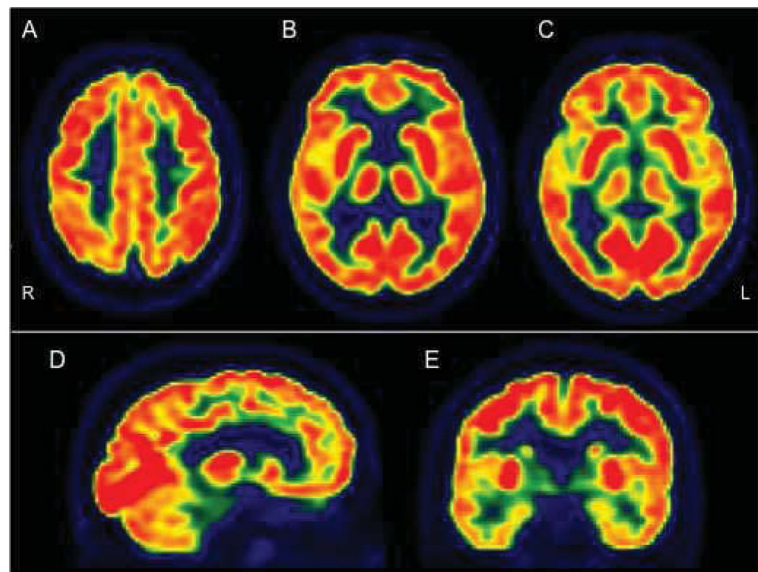


Figure 2.

18F-FDG PET of a normal subject. A, B, C: transaxial plane, showing higher 18F-FDG uptake in basal ganglia, frontal eye fields, posterior cingulate and visual cortices. D: sagittal plane. E: coronal plane, showing lower 18F-FDG activity in temporal lobes, particularly in medial temporal cortex, as compared to the other regions.

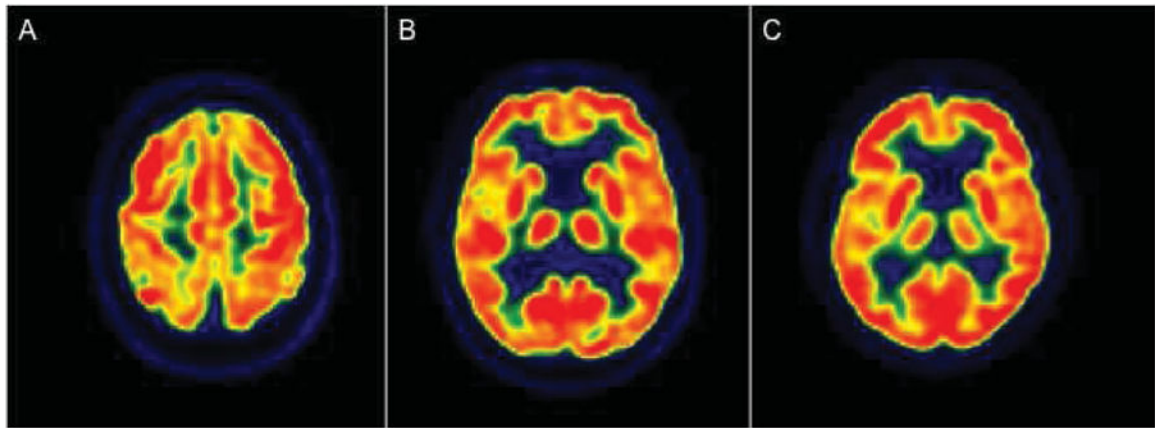


Figure 3.

Age-related metabolic reductions in 3 cognitively normal subjects. A: 80 year-old subject, demonstrating prefrontal and superior parietal hypometabolism with sparing of primary sensory-motor cortices. B: 76 year-old subject, showing mild hypometabolism in anterior cingulate cortex, medial frontal regions and insula. C: 82 year-old subject, demonstrating hypometabolism involving anterior cingulate cortex, medial frontal regions and insula.

Table 1

Summary of literature on the effect of gender on cerebral glucose metabolism in normal healthy subjects.

Study	Men/Women	Mean age (years)(M/W)	18F-FDG PET findings
Hsieh et al. 2012	50/50	58.58/57.56	M>W in bilateral visual cortices and cerebellum
Kim et al. 2009	32/46	46.6/40.6	No differences. M: gender-specific age-related hypometabolism in insula W: gender-specific age-related hypometabolism in caudate nucleus
Brickman et al. 2003	35/35	54.0 (all subjects)	M>W in caudate nucleus
Kawachi et al. 2002	22/22	63.0/63.1	M>W in insula, middle temporal gyrus, medial frontal lobe; W>M in hypothalamus
Willis et al. 2002	38/28	38.1/41.0	W>M (global) W: maximal age-related hypometabolism in mid-superior temporal gyrus; M: maximal age-related hypometabolism in a more superior temporal gyrus;
Volkow et al. 1997	15/13	44/44	W>M in temporal poles and cerebellum
Murphy et al. 1996	55/65	53 (all subjects)	W>M in thalamus M>W in hippocampus
Gur et al. 1995	37/24	27 (all subjects)	M>W in orbitofrontal lobes, temporal poles, temporo-occipital areas, hippocampus and amigdala
Andreason et al. 1994	21/18	26 (all subjects)	W>M in orbitofrontal and medial frontal cortices, posterior cingulate cortex and caudate nucleus
Miura et al. 1990	17/15	30 (all subjects)	No differences.
Yoshii et al. 1988	39/37	54 (all subjects)	W>M (global)
Baxter et al. 1987	7/7	32 (all subjects)	W>M (global)

Data from Refs 20–22,29,36–43.