Functional Brain Imaging

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

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Abbreviations

AAN	American Academy of Neurology
ACR	American College of Radiology
AD	Alzheimer's disease
ADRDA	Alzheimer's Disease and Related Disorders Association
AETMIS	Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé
AHRQ	Agency for Health Research and Quality
ASNR	American Society of Neuroradiology
CCHS	Canadian Community Health Survey
CCTR	Cochrane Controlled Trials Register
Cho	Choline
CI	Confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
Cr	Creatine
CT	Computed tomography
DARE	Database of Abstracts of Reviews of Effectiveness
DAT	Dopamine transporter
DMFP	Dorsal medial prefrontal cortex
ECoG	Electrocortocography
ECRI	ECRI Institute
EEG	Electroencephalogram
ETLE	Extratemporal lobe epilepsy
FDA	Food and Drug Administration
FDG	18F-labelled-fluorodeoxyglucose
FDOPA	fluorodopa
FET	O-(2-^{18}F-Fluoroethyl)-L-Tyrosine
FLE	Frontal lobe epilepsy
FLT	18F-labelled-fluoro-3'-deoxyl-3'-L-fluorothymidine
fMRI	Functional magnetic resonance imaging
FP CIT	Fluoropropyl ß-carbomethoxy-3 ß-4-iodophenyltropane
FTLE	Frontotemporal lobe epilepsy
Gd	Gadolinium
GIN	Guidelines International Network
H&Y	Hoehn & Yahr stage
HTA	Health technology assessment
IBZM	123-iodobenzamide
ICEEG	Intracranial electroencephalogram
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Idiopathic Parkinson's disease
ISMRM	International Society for Magnetic Resonance in Medicine
LILACS	Latin American and Caribbean Health Sciences Literature
LTLE	Lateral temporal lobe epilepsy
MCI	Mild cognitive impairment
MEG	Magnetoencephalography
MET	L-methyl-11C-methionine
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy

MS	Multiple sclerosis
MSA	Multiple system atrophy
MSAC	Medical Services Advisory Committee
MSI	Magnetic source images
MTLE	Mesial temporal lobe epilepsy
N/A	Not applicable
NAA	N-acetylaspartate
NGC	National Guideline Clearinghouse
NHS	National Health Service
NICE	National Institute of Clinical Evidence
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NPHS	National Population Health Survey
NPV	Negative predictive value
NR	Not reported
NTLE	Neocortical temporal lobe epilepsy
OHS	Ontario Health Survey
OLE	Occipital lobe epilepsy
PCS	Prospective cohort study
PD	Parkinson's disease
PET	Positron emission tomography
PLE	Parietal lobe epilepsy
PPV	Positive predictive value
RACLO	11-C-Raclopride
RCT	Randomized controlled trial
RS	Retrospective study
RSNA	Radiological Society of North America
RT	Radiation therapy
SD	Standard deviation
SPECT	Single photon emission computed tomography
TLE	Temporal lobe epilepsy
VATAP	Veterans Affairs Technology Assessment Program
VBM	Voxel-based morphology
UPDRS III	Unified Parkinson's Disease Rating Scale, Motor Function

Executive Summary

Objective

The objective of this analysis is to review a spectrum of functional brain imaging technologies to identify whether there are any imaging modalities that are more effective than others for various brain pathology conditions. This evidence-based analysis reviews magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) for the diagnosis or surgical management of the following conditions: Alzheimer's disease (AD), brain tumours, epilepsy, multiple sclerosis (MS), and Parkinson's disease (PD).

Clinical Need: Target Population and Condition

Alzheimer's disease is a progressive, degenerative, neurologic condition characterized by cognitive impairment and memory loss. The Canadian Study on Health and Aging estimated that there will be 97,000 incident cases (about 60,000 women) of dementia (including AD) in Canada in 2006.

In Ontario, there will be an estimated 950 new cases and 580 deaths due to brain cancer in 2006. Treatments for brain tumours include surgery and radiation therapy. However, one of the limitations of radiation therapy is that it damages tissue though necrosis and scarring. Computed tomography (CT) and magnetic resonance imaging (MRI) may not distinguish between radiation effects and resistant tissue, creating a potential role for functional brain imaging.

Epilepsy is a chronic disorder that provokes repetitive seizures. In Ontario, the rate of epilepsy is estimated to be 5 cases per 1,000 people. Most people with epilepsy are effectively managed with drug therapy; but about 50% do not respond to drug therapy. Surgical resection of the seizure foci may be considered in these patients, and functional brain imaging may play a role in localizing the seizure foci.

Multiple sclerosis is a progressive, inflammatory, demyelinating disease of the central nervous system (CNS). The cause of MS is unknown; however, it is thought to be due to a combination of etiologies, including genetic and environmental components. The prevalence of MS in Canada is 240 cases per 100,000 people.

Parkinson's disease is the most prevalent movement disorder; it affects an estimated 100,000 Canadians. Currently, the standard for measuring disease progression is through the use of scales, which are subjective measures of disease progression. Functional brain imaging may provide an objective measure of disease progression, differentiation between parkinsonian syndromes, and response to therapy.

The Technology Being Reviewed

Functional Brain Imaging

Functional brain imaging technologies measure blood flow and metabolism. The results of these tests are often used in conjunction with structural imaging (e.g., MRI or CT). Positron emission tomography and MRS identify abnormalities in brain tissues. The former measures abnormalities through uptake of radiotracers in the brain, while the latter measures chemical shifts in metabolite ratios to identify abnormalities. The potential role of functional MRI (fMRI) is to identify the areas of the brain responsible for language, sensory and motor function (sensorimotor cortex), rather than identifying abnormalities in tissues. Magnetoencephalography measures magnetic fields of the electric currents in the brain, identifying aberrant activity. Magnetoencephalography may have the potential to localize seizure foci and

to identify the sensorimotor cortex, visual cortex and auditory cortex.

In terms of regulatory status, MEG and PET are licensed by Health Canada. Both MRS and fMRI use a MRI platform; thus, they do not have a separate licence from Health Canada. The radiotracers used in PET scanning are not licensed by Health Canada for general use but can be used through a Clinical Trials Application.

Review Strategy

The literature published up to September 2006 was searched in the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, and International Network of Agencies for Health Technology Assessment (INAHTA). The database search was supplemented with a search of relevant Web sites and a review of the bibliographies of selected papers.

General inclusion criteria were applied to all conditions. Those criteria included the following:

- Full reports of systematic reviews, randomized controlled trials (RCTs), cohort-control studies, prospective cohort studies (PCS'), and retrospective studies.
- Sample sizes of at least 20 patients ($\geq$ 10 with condition being reviewed).
- English-language studies.
- Human studies.
- Any age.
- Studying at least one of the following: fMRI, PET, MRS, or MEG.
- Functional brain imaging modality must be compared with a clearly defined reference standard.
- Must report at least one of the following outcomes: sensitivity, specificity, accuracy, positive predictive value (PPV), receiver operating characteristic curve, outcome measuring impact on diagnostic testing, treatment, patient health, or cost.

Summary of Findings

There is evidence to indicate that PET can accurately diagnose AD; however, at this time, there is no evidence to suggest that a diagnosis of AD with PET alters the clinical outcomes of patients.

The addition of MRS or O-(2-^{18}F-Fluoroethyl)-L-Tyrosine (FET)-PET to gadolinium (Gd)-enhanced MRI for distinguishing malignant from benign tumours during primary diagnosis may provide a higher specificity than Gd-enhanced MRI alone. The clinical utility of additional imaging in patients to distinguish malignant from benign tumours is unclear, because patients with a suspected brain tumour will likely undergo a biopsy despite additional imaging results.

The addition of MRS, FET-PET, or MRI T2 to Gd-enhanced MRI for the differentiation of recurrence from radiation necrosis may provide a higher specificity than Gd-enhanced MRI alone. The clinical utility of additional imaging in patients with a suspected recurrence is in the monitoring of patients. Based on the evidence available, it is unclear if one of the imaging modalities (MRS, FET-PET, or MRI T2) offers significantly improved specificity over another.

There may be a role for fMRI in the identification of surgical candidates for tumour resection; however, this requires further research.

Based on the studies available, it is unclear if MEG has similar accuracy in localizing seizure foci to intracranial electroencephalogram (ICEEG). More high-quality research is needed to establish whether there is a difference in accuracy between MEG and ICEEG.

The results of the studies comparing PET to noninvasive electroencephalogram (EEG) did not demonstrate that PET was more accurate at localizing seizure foci; however, there may be some specific conditions, such as tuberous sclerosis, where PET may be more accurate than noninvasive EEG.

There may be some clinical utility for MEG or fMRI in presurgical functional mapping; however, this needs further investigation involving comparisons with other modalities. The clinical utility of MRS has yet to be established for patients with epilepsy.

Positron emission tomography has high sensitivity and specificity in the diagnosis of PD and the differential diagnosis of parkinsonian syndromes; however, it is unclear at this time if the addition of PET in the diagnosis of these conditions contributes to the treatment and clinical outcomes of patients.

There is limited clinical utility of functional brain imaging in the management of patients with MS at this time. Diagnosis of MS is established through clinical history, evoked potentials, and MRI. Magnetic resonance imaging can identify the multifocal white lesions and other structural characteristics of MS.

Objective

The objective of this analysis is to review a spectrum of functional brain imaging technologies to identify whether there are any imaging modalities that are more effective than others for various brain pathology conditions. This evidence-based analysis reviews magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) for the diagnosis or surgical management of the following conditions: Alzheimer's disease (AD), brain tumours, epilepsy, multiple sclerosis (MS), and Parkinson's disease (PD).

Each condition was reviewed separately investigating each of the imaging modalities. Unique questions were developed for each of the conditions to assess the potential role of functional imaging in each.

Background

Clinical Need: Target Population and Condition

Alzheimer's Disease

Alzheimer's disease is a progressive, degenerative, neurologic condition, characterized by cognitive impairment and memory loss. The progressive condition causes deterioration over 8 to 10 years. Patients with advanced disease have difficulties with basic activities such as eating, dressing, and bladder control. There is no cure for AD; however, there are some drug therapies that can slow disease progression. These drugs include cholinesterase inhibitors, tacrine and donepezil. (1)

The Canadian Study on Health and Aging (2) has been observing the incidence and prevalence of AD since 1991. There will be an estimated 97,000 incident cases (about 60,000 women) of dementia (including AD) in Canada in 2006. (3;4) The estimated prevalence of dementia (including AD) in the Canadian population over 65 years is 435,000 (about two-thirds of these patients have AD). In 2006, there will be an estimated 164,000 people with AD in Ontario. (3) The incidence of AD increases with age. By age 85 years, 1 in 3 Canadians has dementia. (2)

According to the Alzheimer's Society of Canada, (5) the diagnosis of AD involves a systematic assessment including, at least, medical history, mental status examination, and physical examination. Imaging with MRI, computed tomography (CT), single photon emission computed tomography (SPECT), PET, or electroencephalogram (EEG) may also be used in the diagnosis.

Brain Tumour

In 2006, there will be an estimated 2,500 new cases of brain cancer diagnosed in Canada, and an estimated 1,670 deaths due to brain cancer. (6) In Ontario, there will be 950 new cases and 580 deaths due to brain cancer. Statistics Canada (6) has calculated that the 5-year survival ratio was 23% (95% confidence interval [CI], 22%–25%) in brain cancer cases diagnosed between 1995 and 1997. The 5-year survival ratio was 59% for all invasive cancers (95% CI, 59%–60%), with only esophageal (13%), lung (16%), and pancreatic (6%) cancers having a lower 5-year survival ratio than brain cancer. (6)

Primary brain tumours arise from glial cells. There are 4 types of glial cells: astrocytes, oligodendrocytes, microglia, and ependymocytes. Brain tumours are classified by cell type or by World Health Organization grading classification. Grading criteria include cellular atypia, mitoses, infiltration, necrosis, and vascular

changes. Low-grade gliomas are grade I and II, and are typically less aggressively treated than high-grade (grade III–IV) gliomas (e.g., glioblastoma multiforme). Low-grade tumours are less likely to invade surrounding tissue and to recur compared with high-grade tumours. (7)

Currently, the gold standard for the noninvasive diagnosis of primary or recurrent tumours is the use of MRI with gadolinium (Gd). If surgical confirmation is contraindicated or suspicion of radionecrosis is high, then MRS may be considered (personal communication, clinical expert, November 15, 2006).

Treatment for brain tumours typically includes surgery to resect the tumour; however, the entire tumour may not be resected during surgery depending on a variety of factors, including the numbers, size, and location of the tumour. Incomplete resection may be necessary to spare healthy brain tissue surrounding the tumour. Radiation therapy may be used alone or in addition to surgery. More recently, the use of chemotherapy to treat high-grade tumours has resulted in improved survival (personal communication, clinical expert, December 14, 2006).

Radiation therapy can be delivered as whole-brain radiotherapy, conformal 3-dimensional radiotherapy, or stereotactic radiotherapy (targeted high-dose radiation at lesion). However, these therapies are not without limitations. Radiation therapy damages tissue though necrosis and scarring. Computed tomography and MRI may not distinguish between radiation effects and resistant tissue. Thus a potential role of functional brain imaging is to differentiate the cells in the lesions caused by radiation therapy.

Individuals with brain tumours typically have neurological symptoms, and are rarely diagnosed without symptoms of a brain tumour. Diagnostic imaging provides the potential opportunity to avoid unnecessary biopsy, or provide more precision for stereotactic biopsies. Throughout the course of treatment, imaging has the potential to determine response to treatment and manage therapies efficiently. (8)

Epilepsy

Epilepsy is a chronic disorder characterized by repetitive seizures. It may have a variety of etiologies that range from genetic or developmental anomalies, to multiple types of brain trauma (e.g., injury, stroke, or tumour). For some patients, there may be no apparent cause.

Seizures are classified by location focus and etiology.

For most people with epilepsy, their condition is effectively managed with drug therapy; however, about 30% do not respond to drug therapy (personal communication, clinical expert, December 1, 2006). Surgical resection of the epileptic focus is an option for some of these patients. (9)

The rate of epilepsy in Canada is 5.2 cases per 1,000 population (95% CI, 4.9–5.4 cases) based on the results of the 1998–1999 National Population Health Survey (NPHS), and 5.6 cases per 1,000 population (95% CI, 5.1–6.0 cases) based on the results of the 2001 Canadian Community Health Survey (CCHS). (10) In Ontario the rate is 5.0 cases per 1,000 (95% CI, 4.2–5.9 cases) in the NPHS, and 5.2 cases per 1,000 (95% CI, 4.5–6.1 cases) in the CCHS. (10) Thus, there are about 66,000 Ontario residents diagnosed with epilepsy.

Current Practice for Localization of Seizure Foci in Patients with Epilepsy

Patients with refractory epilepsy being considered for surgery must undergo a series of tests to establish the location of the seizure foci. All patients undergo scalp EEG with video monitoring, which is a noninvasive test to localize the seizures. Basically, it involves videotaping the patient while undergoing an EEG. The scalp video EEG monitors patients for a few days (usually 5-10 days) in hospital while a

patient is off their medication to measure several seizures. If a patient does not suffer any seizures in this time, they will continue to monitor the patient for a longer period of time (sometimes up to 1 month). Patients will also undergo a MRI to identify structural abnormalities, and to attempt to correlate structural abnormalities with EEG results. SPECT may also be performed. Patients will also undergo a neuropsychological evaluation to assess if a patient's language, motor or sensory function are affected by their seizures. These results will also be compared with the MRI, EEG and SPECT (if performed) results to identify consistencies. In some cases, as part of the neuropsychological evaluation, patients will also undergo a fMRI for functional mapping.

If, at this point, there is suspicion that the seizures are focal, intracranial EEG (ICEEG) is used to localize the seizure foci. ICEEG is an invasive procedure either involving drilling holes into the skull in order to place electrodes on the brain, or by craniotomy to place a mesh of electrodes (subdural grid) on the brain. Patients remain in hospital for a few days, just like the scalp video EEG, to measure several seizures in order to localize the foci. This procedure involves surgery to place the electrodes, and then another surgery to remove the electrodes, which may or may not be combined with surgery for resection of the seizure foci. If the foci are localized, surgery is considered; if multifocal, surgery is no longer an option.

Surgery for patients with drug-refractory epilepsy is effective in eliminating seizures or significantly decreasing the frequency of seizures. Long-term follow-up studies indicate that 66% of patients with temporal lobe epilepsy are seizure-free 5 years after surgery. (11) Approximately another 20% of patients with have a "worthwhile improvement" in the frequency of seizures. (12)

Multiple Sclerosis

Multiple sclerosis is a progressive, inflammatory, demyelinating disease of the central nervous system (CNS). The cause of MS is unknown; however, it is expected to have a combination of etiologies including genetic and environmental components. (13)

Initial symptoms of MS include optic neuritis, transverse myelitis, double vision, and numbness of the leg. (14) The symptoms associated with MS are not always present, and patients often have periods of remission during which they are free of symptoms. During these periods of clinical silence, the disease continues to progress. One of the proposed advantages of functional brain imaging for MS is that it would allow for earlier diagnosis because, despite a lack of symptoms, there are changes that can be observed, including the formation of new white-matter plaque in the CNS. Earlier diagnosis may allow for earlier initiation of treatment with the intention of delaying disease progression.

Based on results of the CCHS, the prevalence of MS in Canada is 240 cases per 100,000 (95% CI, 210–280 cases). (13) The lowest prevalence of MS provincially in Canada is in Quebec (about 180/100,000), and the highest prevalence is in Atlantic Canada (about 350/100,000). In Ontario the prevalence of MS is estimated to be 230 cases per 100,000 based on CCHS data from 2000/2001. (13)

Parkinson's Disease

Parkinson's disease is the most prevalent movement disorder. It affects an estimated 100,000 Canadians. (15) Parkinson's disease is characterized by bradykinesia (slow, incomplete movements), tremor, rigidity, and impaired balance. Parkinson's disease is a progressive disease that affects an individual's quality of life at each stage of the disease.

Parkinson's disease is caused by a degeneration of dopaminergic neurons that project from the substantia

nigra in the midbrain to the striatal complex in the forebrain. (16) This region is called the nigrostriatal pathway. Essential tremor, vascular parkinsonism, and AD are not associated with the degeneration of the nigrostriatal pathway; thus, imaging of the nigrostriatal pathway can assist in excluding these diagnoses. Idiopathic Parkinson's disease (IPD), progressive supranuclear palsy, multiple system atrophy (MSA), and corticobasal ganglionic degeneration all involve degeneration of the nigrostriatal pathway, thus imaging of the nigrostriatal pathway will not allow differentiation between these conditions. (16)

A clinical pathology study (17) from the United Kingdom in 1992 reported that the diagnostic accuracy for diagnosing IPD was 75%. The remaining 25% of patients diagnosed with IPD had other parkinsonian syndromes or dementia. In 2001, the same group of authors (18) reported that the diagnostic accuracy for IPD was 90%, indicating that clinicians had improved their ability to distinguish IPD from other neurological conditions since 1992. It is important to note that in the updated study, patients had end-stage disease, which may have made it easier to achieve an accurate diagnosis. Thus, 90% accuracy reflects a "best-case" scenario, and is unlikely to represent the norm. (16)

Currently, the standard for measuring disease progression is through the use of scales (e.g., Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr's, modified Columbia score, etc.), which are subjective measures of disease progression. (19) One of the proposed advantages of using PET in patients with PD is that it can be an objective measure of diagnosis, disease progression, or assessing the efficacy of drugs. (20)

New Technology Being Reviewed

Functional Brain Imaging

Functional brain imaging technologies measure blood flow and/or metabolism. The results are often used in conjunction with structural imaging (i.e., MRI or CT). Unlike CT and MRI, functional brain imaging modalities, such as PET, MRS, and fMRI, can isolate areas with changes in activity prior to structural change.

Positron Emission Tomography

Positron emission tomography uses radioactive tracer isotopes attached to metabolically active molecules (e.g., glucose) to investigate functionality in the body. Briefly, PET generates an image when positrons are released from the nuclei of the radiotracers. Once released, the positrons collide with negatively charged electrons. When a positron and an electron collide, this causes annihilation, whereby both the positron and electron are converted into energy. This energy is divided between 2 photons traveling 180 degrees from each other. The released photon pair can be detected as a line—these lines are called "coincidence events." A group of coincidence events are used to generate a sinogram, which is used to create PET images. (21)

Positron emission tomography scans can be used in conjunction with structural imaging modalities, such as CT or MRI, and PET can be used in a variety of settings, including in cancer imaging, heart function studies, and brain imaging.

Radiopharmaceuticals have varying half-lives (time to decrease radioactivity by half). Table 1 lists the half-lives of some of the radiopharmaceuticals used in PET imaging. A cyclotron is needed to create radiopharmaceuticals. The radiopharmaceuticals are incorporated into the metabolically active molecules

(e.g., glucose).

Table 1: Radiopharmaceuticals Used in Studies of Positron Emission Tomography

Radiopharmaceutical		Examples of Radiotracers	Half-Life, Minutes
18-Fluorine	FDG	18F-labelled-fluorodeoxyglucose	~110
	FET	O-(2-^{18}F-Fluoroethyl)-L-Tyrosine	
	FLT	18F-labelled-fluoro-3'-deoxy-3'-L-fluorothymidine	
11-Carbon	MET	L-methyl-11C-methionine	~20
13-Nitrogen		N-13 ammonia	~10
15-Oxygen		O-15 water	~2

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging is also called blood oxygenation level-dependent MRI. Functional magnetic resonance imaging images neuronal activity through blood flow (oxyhemoglobin delivery) which increases with brain activity and measures activity in the sensorimotor cortex, such as language, sensory, and motor function. Functional magnetic resonance imaging uses the MRI platform to generate functional images of the brain. There is no radiation exposure associated with fMRI, and it can be performed on a standard MRI system after a software upgrade.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy uses a MRI system to measure the concentration of several metabolites in the brain. Magnetic resonance spectroscopy distinguishes the chemical properties of a certain area of the brain relative to the surrounding areas. Magnetic resonance spectroscopy detects different chemicals by their different vibration frequencies, creating a chemical shift. Commonly measured metabolites include N-acetyl acetate (NAA), myoinositol, choline (Cho), and creatine (Cr).

One of the potential limitations of MRS is that it may not be able to distinguish patients with tissues with mixed histological findings. For instance, in patients with suspected tumour recurrence, MRS may be able to distinguish pure tumour tissue from pure necrosis tissue; however, many patients will have mixed histological findings with both tumour tissue and necrosis tissue, limiting the utility of MRS. (22)

Magnetoencephalography

Magnetoencephalography is a noninvasive imaging modality that measures the magnetic fields of the electric currents in the brain, that is, it measures the electromagnetic activity in the brain. The small magnetic fields are detected by superconducting quantum interference devices. The information gathered from the superconducting quantum interference devices is analyzed and typically fused with a structural image (e.g., MRI). The resultant MEG on MRI images can also be referred to as Magnetic source images (MSI). Magnetoencephalography has a 2 to 3 millimeter spatial accuracy and the ability to identify brain activity in real time, unlike fMRI, MRI, PET, CT, and SPECT. (23)

Advantages of Magnetoencephalography:

➢ Superior temporal resolution (milliseconds) compared with fMRI, MRI, PET, CT, and SPECT
➢ Does not require strong external magnetic fields like fMRI
➢ Does not require injections of radiotracers

Potential roles of Magnetoencephalography:

➢ To identify sensorimotor cortex in presurgical patients
➢ To localize epileptic foci in presurgical patients

The first MEG system was housed in a protected (shielded) room at the Massachusetts Institute of Technology (MIT). In 1968, Dr. David Cohen performed the first MEG at MIT. (24)

In 2000, the Hospital for Sick Children in Toronto, Ontario, installed the first clinical MEG site in Canada (and the first in the world to be installed in a pediatric institution). (25)

Alternative Technologies

Alternative imaging technologies include CT, MRI, ultrasound, and SPECT. Computed tomography and MRI create structural images; they do not measure function. In most cases, functional brain imaging will be used in conjunction with CT or MRI. Single photon emission computed tomography uses standard nuclear medicine cameras, which are available in every hospital. At many centres, ictal SPECT with Tc-99m hexamethylpropylene amine oxime is the standard of care for the evaluation of epilepsy (personal communication, clinical expert, December 11, 2006).

An alternative to MEG in patients with epilepsy is ICEEG. Intracranial electroencephalogram includes electrocorticography (subdural grid placement) and the placement of depth electrodes on the brain. Intracranial electroencephalogram is the gold standard for localizing epileptic foci. Intracranial electroencephalogram is an invasive procedure either involving drilling holes into the skull in order to place electrodes on the brain, or by craniotomy to place a mesh (subdural grid) of electrodes on the brain. The grid is connected to a portable EEG to measure electrophysiology to identify the seizure foci. Patients undergoing this procedure are required to remain in hospital for a few days under observation for seizures, and then if the epileptic foci are localized, surgery is considered. This is a highly invasive procedure that involves 2 surgeries, one to implant the grid or place electrodes, and then another to remove the grid or electrodes. Intracranial electroencephalogram involves patient discomfort and the potential risk of complications (personal communication, clinical expert, October 27, 2006).

Although ICEEG is the accepted gold standard, it has limitations. In 1995, Cascino et al. (26) retrospectively reviewed the results of 30 patients undergoing presurgical evaluation for localization of seizure foci. The patients had undergone ICEEG monitoring, and the decision regarding the localization of the seizure foci was based on multiple recorded seizures. Cascino and colleagues reported 1-year follow-up data on 21 patients. Of these 21 patients, 9 were seizure-free, 3 reported t least a 95% improvement in seizures, 4 reported at least a 50% improvement in seizures, and 5 reported minimal improvement or no change. Thus, about 57% of patients had success with surgery based on results of the ICEEG.

In another study by Weinand et al., (27) 36 patients underwent surgery for the resection of seizure-foci after ICEEG. At 1 year, 23 (64%) patients were seizure-free, 9 (25%) were significantly improved, 3 (8%) were improved, and 1 (3%) patient was unchanged. Thus, based on the results of these studies, the range of surgical success (seizure-free or significantly improved) based on ICEEG results ranged from 57% to 89%.

Currently, the standard procedure for presurgical functional mapping is the intracarotid sodium amobarbital procedure (known as the ISAP or the Wada test), which maps language and memory on each side of the brain. Prior to the Wada test, patients underwent a cerebral angiogram to assess blood flow in

the brain by using a catheter threaded through the femoral artery to the carotid artery, to inject dye into the arteries in the brain.

During a Wada test, sodium amobarbital is injected into the right or left carotid artery (an injection in the right carotid artery will numb the right side of the brain and vice-versa). Patients are then stimulated with objects and pictures to assess cognitive function. When the sodium amobarbital wears off on one side of the brain, the procedure is repeated on the other side. Due to the insertion of the catheter, the Wada test is considered an invasive procedure. Functional brain imaging through fMRI or MEG has the potential to provide information similar to the Wada test without the invasiveness of the catheter.

Regulatory Status

There are a few companies that manufacture PET systems that are licensed by Health Canada. The PET systems are not licensed for specific indications. They are intended to be used to image and measure the distribution of injected radiopharmaceuticals. The radiotracers used in PET scanning are not licensed by Health Canada for general use but can be used through a clinical trials application, which are submitted to Health Canada when researchers want to conduct clinical trials with drugs in humans.

There are 2 MEG systems licensed by Health Canada. They are licensed to identify locations of visual, auditory, somatosensory, and motor cortex in the brain; the MEG systems are not licensed to be used for a specific patient population with a specified condition.

There are no unique licences from Health Canada for MRS and fMRI, because both of these technologies use a MRI platform. Magnetic resonance imaging systems are licensed by Health Canada. Most new MRI systems have MRS and fMRI capability if additional software is purchased (or may be included with the MRI purchase price) (personal communication, clinical expert, August 10, 2006).

Literature Review on Effectiveness

It is important to define how the effectiveness of functional brain imaging for the diagnosis of AD, brain tumours, epilepsy, MS, or PD will be assessed. The Medical Advisory Secretariat was primarily interested in how the accuracy of the various imaging modalities has an impact on clinical or patient outcomes, compared with the current standard of diagnosis or presurgical evaluation.

Measuring Accuracy

For the purpose of this review, the following formulas are being used for sensitivity, specificity, PPV, and negative predictive value (NPV).

Sensitivity = true positives / (true positives + false negatives)
Specificity = true negatives / (true negatives + false positives)

Positive predictive value = true positives / (true positives + false positives)
This refers to the probability that a patient with positive test results actually has the condition. Positive predictive value depends on the prevalence of the condition in the population being tested.

Negative predictive value = true negatives / (true negatives + false negatives)
This refers to the probability that a patient with negative test results is truly free of the condition. Negative predictive value depends on the prevalence of the condition in the population being tested.

Research Questions

The questions that this review aims to answer have been formatted in Table 2. Each condition has a different question or questions. The years included in the literature search vary across conditions and imaging modalities because this was dependent on the timing of the most recent health technology assessment reviewing functional brain imaging for each condition.

Table 2: Question, Patient Population, and Years Searched for Literature for Each Condition Being Reviewed*

Condition	Question(s)	Patient Population	Years Searched†
Alzheimer's disease	What is the potential role of functional brain imaging in the diagnosis of Alzheimer's disease?	Patients with suspected AD	PET, MRS, fMRI: 2004–Sep. 2006 MEG: 1966–Sep. 2006
Brain tumour	What is the potential role of functional brain imaging: ➢ in the detection and grading of primary tumours? ➢ in the differentiation of recurrence from radiation necrosis? ➢ in the selection of surgical candidates for tumour resection?	Patients with suspected brain tumour or suspected recurrence	PET: 2003–Sep. 2006 MRS: 2005–Sep. 2006 fMRI, MEG: 1966–Sep. 2006
Epilepsy	What is the potential role of functional brain imaging: ➢ in the localization of seizure foci in people with refractory epilepsy being considered for surgery? ➢ In the presurgical functional mapping of people with refractory epilepsy being considered for sugery?	Patients with refractory epilepsy being considered surgery	PET, MRS: 2004–Sep. 2006 MEG: 2003–Sep. 2006 fMRI: 1966–Sep. 2006
Multiple sclerosis	What is the potential role of functional brain imaging in the diagnosis of multiple sclerosis?	Patients with suspected MS	PET, MRS, fMRI, MEG: 1966–Sep. 2006
Parkinson's disease	What is the potential role of functional brain imaging: ➢ in the diagnosis of Parkinson's disease? ➢ In the diagnosis of other parkinsonian syndromes?	Patients with suspected PD or the differentiation of parkinsonian syndromes	PET, MRS, fMRI: 2001–Sep 2006 MEG: 1966–Sep 2006

*AD indicates Alzheimer's disease; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; MS; multiple sclerosis; PD, Parkinson's disease; PET, positron emission tomography.
†The decision regarding which years to search was based on the availability of previous health technology assessments. The search for this review began at the time where the search for the most recent health technology assessment ended.

Methods

Diagnostic studies differ from treatment studies in their design and the outcomes that can be reported. Demonstrating effectiveness and clinical utility of a diagnostic test can be more challenging than demonstrating effectiveness of a treatment, because it can be difficult to measure whether the diagnostic method has an impact on patient outcomes. In 1991, Fryback and Thornbury (28) proposed a hierarchical model of the efficacy for diagnostic tests, describing the complexity of diagnostic studies. Table 3 describes the model.

Table 3: Hierarchy of Diagnostic Evaluation for Assessing Epilepsy With Functional Brain Imaging

Level	Description	Examples of Outcomes Reported
1	Technical feasibility and optimization	➢ Ability to produce consistent outcomes ➢ Resolution of image ➢ Gray-scale range ➢ Reproducibility of image
2	Diagnostic accuracy	➢ Sensitivity and specificity ➢ Diagnostic accuracy ➢ Positive and negative predictive value ➢ Receiver operating characteristic curve
3	Diagnostic thinking impact	➢ Percentage of times clinicians' assessment changed after the test ➢ Percentage of cases where the diagnostic test was determined to be useful in making the diagnosis or differential diagnosis
4	Therapeutic choice impact	➢ Percentage of times therapy planned before diagnostic test changed after the test ➢ Percentage of times the diagnostic test was determined to be useful in planning patient management/treatment
5	Patient outcome impact	➢ Percentage of patients who improved with diagnosis with diagnostic test compared with those diagnosed without the diagnostic test ➢ Morbidity (or additional procedures) avoided after diagnostic test
6	Societal impact	➢ Cost analyses

Source: Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Medical Decision Making 1991; 11:88–94

The purpose of this review is to investigate the clinical utility of functional brain imaging in patients with AD, brain tumours, epilepsy, MS, or Parkinson's disease. Because the focus is on clinical utility, the added clinical information that would be provided by Level 1 studies (i.e., studies of technical feasibility) is limited. For this reason, Level 1 studies were not included in this review; only studies in Levels 2 to 6 were eligible for inclusion.

Inclusion Criteria

General inclusion criteria were applied to all conditions. These criteria include the following:

➢ Full reports of systematic reviews, RCTs, cohort-control studies, prospective cohort studies, retrospective studies;
➢ Samples of at least 20 patients ($\geq$ 10 with condition being reviewed);
➢ English-language studies;
➢ Human studies;
➢ Any age;
➢ Studying at least 1 of the following functional brain imaging modalities: fMRI, PET, MRS, MEG;
➢ Functional brain imaging modality must be compared with a clearly defined reference standard;
➢ At least Level 2 on the Fryback and Thornbury hierarchy; and (28)
➢ Must report at least one of the following outcomes: sensitivity, specificity, accuracy, PPV, receiver operating characteristic curve, outcome measuring impact on diagnostic testing, treatment, patient health, or cost.

Exclusion Criteria

Regardless of condition, studies were excluded if they were:

➢ Level 1 studies (technical feasibility) based on the Fryback and Thornbury model; (28)
➢ Editorials, letters, case reports, abstracts;
➢ Non-English-language studies;
➢ Studies including only normal, healthy individuals; or
➢ Studies reporting only technical feasibility of imaging without providing clinical or diagnostic results.

Results of Literature Review

Summary of Existing Health Technology Assessments

Table 4 describes the health technology assessments and systematic reviews identified that reviewed functional brain imaging for AD, brain tumours, epilepsy, and Parkinson's disease. There were no health technology assessments or systematic reviews identified that reviewed functional brain imaging for patients with suspected or confirmed MS. Most health technology assessments and systematic reviews investigated the use of PET; 4 reviews specifically reviewed MRS (3 for patients with suspected brain tumours, and 1 for the differential diagnosis of parkinsonian syndromes), and 1 health technology assessment reviewed the use of MEG in patients with epilepsy.

There were 4 health technology assessments identified that investigated the role of PET in patients with epilepsy: one by the National Health Service (NHS) in the United Kingdom (9), one by the Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé, (AETMIS) in Canada (29) and 2 by the Medical Services Advisory Committee (MSAC) in Australia. (30;31)

The most recent review by the NHS (9) in 2006 incorporated various neuroimaging technologies including PET, MRS, and SPECT. It did not include MEG or fMRI. Based on their thorough review of the literature, they concluded that the limitations of the neuroimaging studies identified "…did little to inform clinical practice."

The first health technology assessment by MSAC (31) was published in 2000, and reviewed PET for various indications, including epilepsy. Based on this review they concluded that some patients with refractory epilepsy may benefit from presurgical PET scans; however, it was unclear if PET scans could benefit all patients with refractory epilepsy. In 2004, MSAC (30) published a health technology assessment on the use of PET specifically in patients with epilepsy. Despite a lack of high-quality evidence and substantial limitations with the available evidence (including inconsistency in defining a reference standard and assuming that PET results alter patient management without evidence), MSAC concluded that PET scans are clinically useful in patients with refractory epilepsy, where there are inconsistent results on structural imaging and EEG.

The 2001 health technology assessment by AETMIS (29) made a similar conclusion to MSAC.

In addition to the health technology assessments presented in Table 4, in 1999 INAHTA (32) published a review of systematic reviews investigating the role of PET for various conditions and indications. They grouped the systematic reviews into 3 main categories: neuropsychiatry, cardiology and oncology (non-CNS tumours). The category of neuropsychiatry included AD, PD, epilepsy, brain tumours,

cerebrovascular disorders, other neurodegenerative disorders, and other neuropsychiatry conditions. Between 1990 and 1999, they identified 13 systematic reviews by 10 health technology assessment organizations investigating one or a combination of the aforementioned neuropsychiatry conditions. The INAHTA review reported that most of the studies included in the systematic reviews used 18F-labelled-fluorodeoxyglucose (FDG)-PET to study glucose metabolism.

Three of the systematic reviews identified included studies of patients with brain tumours. According to the INAHTA review, the 3 systematic reviews were not able to demonstrate an added benefit of PET in the management of patients with brain tumours. Based on the limited evidence available, they reported that SPECT was superior to PET, while CT and MRI were inferior to PET for the differentiation between brain tumour recurrence and radiation necrosis. There was a paucity of high-quality controlled studies available to review effectively the evidence on the use of PET in patients with suspected brain tumours.

The INAHTA review identified 8 health technology assessments and systematic reviews on the clinical utility of PET in the management of epilepsy. Diagnostic imaging is most frequently used in patients with intractable epilepsy undergoing presurgical evaluation to identify the epileptogenic foci and to determine resectability. Among the 8 reviews, there were conflicting reports on study quality; however, all of the reviews' authors agreed that there was insufficient evidence to support replacing ICEEG or MRI with PET. The review reported that more high-quality evidence was required on the clinical utility of PET for epilepsy.

Table 4: Description of Systematic Reviews and Health Technology Assessments of Functional Brain Imaging*

HTA/ Systematic Review	Question(s)	Years	Sources Searched†	Inclusion Criteria	# of Studies Included	Authors' Conclusions
Alzheimer's dementia						
Matchar et al., 2004 (AHRQ) (33)	1. What are the new clinical data on the use of PET in the diagnosis of early dementia in elderly patients published since 2001? 2. What clinical data are available on the use of SPECT, volumetric CT/MRI, fMRI and MRS in the diagnosis of early dementia in elderly patients, published after 1995?	2001– Jan 2004 for PET 1995– Jan 2004 for other imaging	MEDLINE, INAHTA, NICE, GIN, HTA database (NHS)	● > 2 in the Fryback and Thronbury classification scheme (28) ● Articles comparing AD patients with normal controls were excluded	4 for PET 12 for SPECT 2 for fMRI 4 for MRS 9 for CT/MRI	There is insufficient evidence to revise conclusions from 2001 AHRQ report. (34)
Patwardhan et al., 2004 (35)	What is the role of PET in the diagnosis of AD?	1989– 2003	MEDLINE, CINAHL, HealthSTAR	● English ● Human subjects ● Primary data ● $\geq$12 subjects ● Reference standard ● Data to input 2x2 table—(i.e. includes patients with and without AD and +/- PET results)	15	Sensitivity and specificity is limited by study design and patient characteristics—the clinical value of these parameters is uncertain.
Gill et al., 2003 (36)	What incremental diagnostic value does PET provide in the evaluation of patients with suspected dementia?	1975– Jan 2001	MEDLINE, Cochrane Library, HTAs	● Use of dedicated PET scanners in the diagnosis of AD	16 original reports 7 HTAs	There is little evidence to support the addition of PET to the routine clinical evaluation of patients with suspected or established dementia.
ECRI, 2002 (37)	What is the role of PET in the diagnosis of AD?	NR	NR	● Diagnosis or screening for AD	12	PET can accurately diagnose AD, however, the effect on patient outcomes is unclear
Matchar et al., 2001 (AHRQ) (34)	1. For patients with AD, can PET be used to determine the type of dementia? 2. For patients with MCI, can PET be used to identify patients will a high probability of developing AD?	1995– 2001	MEDLINE, HealthSTAR, CINAHL	● English, not abstracts ● $\geq$12 patients ● Reference standard ● Data to input 2x2 table— (i.e. includes patients with and without AD and +/- PET results)	18	PET improves the overall accuracy of diagnosis compared with accuracy of an examination based of AAN guidelines. Treatment based on AAN examination guidelines leads to better health outcomes than treatment based on PET results.
AETMIS, 2001 (29)	What is the role of PET in the diagnosis of AD?	1999– 2001	MEDLINE, EMBASE, CancerLit, Cochrane library	● $\geq$10 patients ● Using FDG-PET ● Studies were excluded if they did not include sufficient information to assess the comparability of the cohort and control	2	In AD, the clinical utility of PET is not recognized.
Adams et al., 1998 (VATAP) (38)	What is the role of PET in the diagnosis of AD?	NR	NR	● $\geq$12 patients ● English ● Studies using dedicated PET systems, using FDG-PET ● Not a duplicate study	8 (for AD)	Evidence does not support the use of PET as a diagnostic test for AD

HTA/ Systematic Review	Question(s)	Years	Sources Searched†	Inclusion Criteria	# of Studies Included	Authors' Conclusions
Brain tumour						
Hollingworth, 2006 (39)	Primary focus—update to previous HTAs. No questions explicitly stated	Jan 2002 – Dec 2004	MEDLINE, EMBASE, Cochrane Library	• Assessed diagnostic performance (e.g. sensitivity or specificity) or impact of MRS on subsequent diagnostic testing, treatment choices, patient health or cost-effectiveness of care • $\geq$10 patients with suspected tumours get MRS	22	The evidence is promising, however, more high quality studies are required for policy makers to make decisions.
AHRQ, 2004 (40)	1. How does the diagnostic test performance of FDG-PET compare to conventional imaging alone with respect to the following situations in primary brain tumours: --in performing guided lesion biopsy of recurrent low-grade brain tumours in patients with an indeterminate MRI? --in distinguishing high-grade from low-grade tumours and distinguishing tumour from radiation necrosis in recurrent brain lesions? 2. How does the diagnostic test performance of FDG-PET compare to biopsy alone in the initial grading of the degrees of malignancy for patients with primary brain tumours when the initial biopsy results was indeterminate grade II/III?	1966– April 2003	MEDLINE	• English • $\geq$12 patients	8	There is insufficient evidence to answer the questions posed.
AHRQ, 2003 (41)	1. For what metabolic profiles does MRS provide equivalent, complementary, or more accurate diagnostic information for initial diagnosis, recurrence, or assessing therapy than brain biopsy, conventional anatomic imaging studies or MRS + conventional anatomic imaging vs. biopsy? 2. Does the use of MRS lead to an improved net health outcome by: avoiding unnecessary biopsy, obtaining appropriate biopsy, from appropriate location, directing biopsy to an appropriate location, receiving appropriate treatment, avoiding an inappropriate treatment? 3. Are voxel positions and operator error important factors in obtaining images?	1966– Oct 2002	MEDLINE, INAHTA, NGC, and abstracts from 2001– 2002 professional society proceedings for ASNR, RSNA, and ISMRM	• MRS on patients with suspected or known brain tumours • $\geq$6 patients in vivo • Studies of hydrogen proton MRS	96 (85 studies of technical feasibility)	There is a paucity of high quality direct evidence demonstrating an impact of MRS on diagnostic thinking and therapeutic decision making.
Blue Cross, Blue Shield Association, 2003 (42)	1. Does the evidence demonstrate the sensitivity and specificity of MRS for differentiating neoplastic from	1966– May 2003	MEDLINE, ACR contacted, reference lists of pertinent	• $\geq$10 patients • Method of confirmation of MRS diagnosis • Specified criteria for a	7	MRS for the evaluation of suspected brain tumour does not meet the criteria in order to

HTA/ Systematic Review	Question(s)	Years	Sources Searched†	Inclusion Criteria	# of Studies Included	Authors' Conclusions
	non-neoplastic lesions? 2. Does the evidence demonstrate whether MRS improves net health outcomes when used to differentiate neoplastic from non-neoplastic lesions?		reviews	positive test • Data available to calculate diagnostic test performance		recommend coverage.
ECRI, 2002 (7)	Can positron imaging be used to identify and/or characterize tumours that may recur after cancer treatment?	1964–July 2002	Cancerlit, MEDLINE, Cochrane Library, ECRI databases, CMS, NHS, FDA, NGC Web sites	• English, full reports • Compares PET or SPECT to reference standard • Reports sensitivity and specificity (or sufficient data to calculate) • No pre-treated patients • $\geq$10 patients	6 met inclusion criteria for PET, 7 for SPECT	There is insufficient evidence to conclude that PET or SPECT imaging is better than other modality for the diagnosis of recurrent brain tumours.
AETMIS, 2001 (29)	What is the role of PET in the diagnosis and management of brain tumours?	1999–2001	MEDLINE, EMBASE, CancerLit, Cochrane library	• $\geq$10 patients • Using FDG-PET • Studies were excluded if they did not include sufficient information to assess the comparability of the cohort and control	9	The clinical utility of PET is recognized for evaluating residual lesions after treatment of a recurrent glioma and differentiating between radionecrosis and recurrence in patients with radiation therapy who have abnormalities on diagnostic imaging. It may have a role in the future for diagnosis, staging and grading of tumours.
MSAC, 2000 (31)	What is the role of PET in the detection of residual/recurrent mass in patients treated for malignant glioma?	1966–Jan. 2000	MEDLINE, Cochrane library, HTA Web sites	• Recurrent glioma (not primary) • Evaluated diagnostic accuracy or patient outcomes	21	There is insufficient evidence to conclude that PET is superior to SPECT in differentiating radionecrosis from recurrence.
Epilepsy						
NHS, 2006 (Whiting et al.) (9)	1. Effectiveness and/or accuracy of imaging the seizure focus in people with refractory epilepsy 2. Ability of different imaging to predict patient outcomes following surgery 3. Effectiveness and/or accuracy of imaging refractory epilepsy in the following subgroups: i: people for whom a structural abnormality has been previously identified; ii: people for whom no structural abnormality has been previously identified; iii: people for who EEG recording has isolated a seizure focus; iv: people for whom EEG recording has failed to isolate a seizure focus 4. Cost-effectiveness of imaging	1986–Dec. 2003	MEDLINE, EMBASE, BIOSIS, Pascal, Science Citation Index, LILACS Hand searched the following journals: *Epilepsia, Neurology, Epilepsy Research, Seizure, Brain*	• Adults and children with refractory epilepsy being considered for surgery • $\geq$20 patients • Neuroimaging technique including MRS, fMRI or PET (did not include MEG)	94	There is insufficient evidence on effectiveness and cost-effectiveness of imaging techniques in the work-up for epilepsy surgery to inform clinical practice.
MSAC, 2004 (30)	What is the value of PET prior to surgery in patients with refractory epilepsy where there is no focus with concordant results on usual	1999–June 2004	MEDLINE, EMBASE, Cochrane Library, Current Contents, Pre-	• Patients with refractory epilepsy being considered for surgery and prior MRI and EEG were insufficient	12	In patients where there is no focus with concordant results on usual structural imaging and EEG, PET is safe,

HTA/ Systematic Review	Question(s)	Years	Sources Searched†	Inclusion Criteria	# of Studies Included	Authors' Conclusions
	structural imaging and EEG?		MEDLINE, CINAHL, DARE, CCTR, HTA databases	• FDG-PET studies only • English • Outcomes: diagnostic accuracy, localization rates, safety, costs		provides localizing information and is likely cost-effective over the long-term.
Blue Cross Blue Shield, 2003 (43)	1. Does the evidence demonstrate whether MEG/MSI is able to localize: i) epileptic foci as well as ICEEG or ECoG testing? ii) functional anatomic regions as well as invasive methods of functional testing? 2. Does the evidence demonstrate whether MEG/MSI improves net health outcomes when used to: i) localize seizure foci for resection ii) localize functional anatomic regions to avoid during resection?	1995–July 2003	MEDLINE	• MEG/MSI were being used for localization of seizure focus or presurgical functional mapping • $\geq$10 patients • MEG/MSI was compared with an appropriate reference standard	13	MEG/MSI for presurgical localization of seizure foci does not meet the criteria to recommend coverage. *The national Blue Cross Blue Shield does not cover MEG, however, some state-run Blue Cross Blue Shield organizations do cover MEG (personal communication, November 17, 2006).
AETMIS, 2001 (29)	What is the value of PET prior to surgery in patients with refractory epilepsy?	1999–2001	MEDLINE, EMBASE, CancerLit, Cochrane library	• $\geq$10 patients • Using FDG-PET • Studies were excluded if they did not include sufficient information to assess the comparability of the cohort and control	5	In refractory epilepsy, the clinical utility of PET is recognized for localizing epileptogenic foci in patients with refractory epilepsy being considered for surgery, and where inconclusive localizing information is provided by standard assessment, including seizure semiology, EEG and MRI.
MSAC, 2000 (31)	What is the value of PET prior to surgery in patients with refractory epilepsy?	1966–January 2000	MEDLINE, Cochrane library, HTA Web sites	• Patients with refractory epilepsy being considered for surgery	5	Patients undergoing surgery may benefit from a PET scan, however, it is unclear if PET will benefit all patients with refractory epilepsy.
Parkinson's disease						
Tolosa et al., 2006 (44)	What is the most appropriate method for diagnosing PD? Methods investigated included: drug challenge, olfactory testing, clinical neurophysiology, ultrasound, CT, MRI, SPECT, and PET	1966–2005	MEDLINE, hand searches of citations from previous reviews	• English	unclear	Clinical diagnosis is still the gold standard even though up to 30% of patients with parkinsonism will be reclassified. SPECT and PET could improve the differential diagnosis of parkinsonism, however, the cost-effectiveness of this has yet to be established.
AHRQ, 2003 (45)	What are the results of neuroimaging studies or other diagnostic tests in determining the diagnosis of PD?	1990–2000	MEDLINE, Current Contents, Cochrane Library	• English • Human subjects • $\geq$10 patients	10	Evidence regarding PET & SPECT is inconsistent. MRI may be able to rule out other conditions, NOT useful for diagnosing PD.
Clarke & Lowry, 2001 (46)	The differential diagnosis of parkinsonian syndromes with MRS	1966–1999	MEDLINE	• Includes control group • Proton MRS (not phosphorus)	11 groups of authors	No clear conclusions could be drawn from the heterogeneous results.

* AD indicates Alzheimer's disease; CT, computed tomography; ECoG, electrocortography; EEG, electroencephalogram; FDA, Food and Drug Administration; FDG, 18F-labelled-fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; HTA, health technology

assessment; ICEEG, Intracranial electroencephalogram; MCI, mild cognitive impairment; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MSI, magnetic source images; NR, not reported; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single photon emission computed tomography.
†Sources searched: AAN indicates American Academy of Neurology; ACR, American College of Radiology; AHRQ, Agency for Health Research and Quality; ASNR, American Society of Neuroradiology; CINAHL, Cumulative Index to Nursing & Allied Health Literature; CCTR, Cochrane Controlled Trials Register; CMS, Centers for Medicare & Medicaid Services; DARE, Database of Abstracts of Reviews of Effectiveness; ECRI, ECRI Institute; GIN, Guidelines International Network; HealthSTAR, Health Services Technology, Administration, and Research; ISMRM, International Society for Magnetic Resonance in Medicine; INAHTA, The International Network of Agencies for Health Technology Assessment; LILACS, Latin American and Caribbean Health Sciences Literature; MSAC, Medical Service Advisory Committee; NGC, National Guideline Clearinghouse; NHS, National Health Service; NICE, National Institute of Clinical Evidence; RSNA, Radiological Society of North America; VATAP, Veteran Affairs Technology Assessment Program.

The review by Tolosa et al. (44) summarized the usefulness of various strategies for diagnosing PD. They concluded that drug challenge and MRI were useful in routine practice for making differential diagnoses of parkinsonism, and that SPECT was useful in routine practice in the early diagnosis of PD. Positron emission tomography was deemed to be of limited clinical use at this time, and further research was required to attempt to establish a role for PET in the diagnosis of PD (Table 5).

Table 5: Role of Diagnostic Techniques in Parkinson's Disease*

Diagnostic Test	Early Diagnosis	Differential Diagnosis	Available in Ontario
Drug challenge	Not useful	Useful in routine practice	Yes
CT	Not useful	Limited use	Yes
MRI	Not useful	Useful in routine practice	Yes
SPECT–DAT	Useful in routine practice	Limited use	Yes
SPECT–IBZM	Not useful	Limited use	Yes
PET–FDOPA	Limited use	Limited use	Restricted
PET–FDG	Not useful	Limited use	Restricted
PET–RACLO	Not useful	Limited use	Restricted

*CT refers to computed tomography; DAT, dopamine transporter; FDOPA, fluorodopa; FDG, 18F-labelled-fluorodeoxyglucose; IBZM, 123-iodobenzamide; MRI, magnetic resonance imaging; PET, positron emission tomography; RACLO, 11-C-Raclopride; SPECT, single photon emission computed tomography.

Reprinted from Lancet Neurology, 5(1), Tolosa E, Wenning G, Poewe W., The diagnosis of Parkinson's disease, pp 75–86, Copyright 2006, with permission from Elsevier.

Summary of Medical Advisory Secretariat Review of Functional Brain Imaging

The literature review did not identify any RCTs that studied the clinical utility of functional brain imaging in the management or diagnosis of patients with any of the conditions being reviewed. Table 8 lists the level of evidence and number of studies identified.

Table 6: Level of Evidence of Included Studies*

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic reviews of RCT	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	4
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	1
Case series (multisite)	4b	22
Case series (single site)	4c	0
Retrospective review, modeling	4d	14
Case series presented at international conference	4(g)	0

*g indicates grey literature; RCT, randomized controlled trial.

In addition to determining the level of evidence, studies were also classified according to the hierarchy of diagnostic evaluation defined by Fryback and Thronbury. (28) Examples of each level in the hierarchy are described in Table 3. Table 7 outlines the number of studies identified for this review according to the hierarchy. It is important to note that level 1 studies (i.e., technical feasibility studies) were not eligible for inclusion in this review.

Table 7: Hierarchy of Diagnostic Evaluation and the Number of Studies Available for Assessing the Diagnosis of Parkinson's Disease*

Level	Description	Number of Studies (References)				
		Alzheimer's Disease	Brain Tumour	Epilepsy	Multiple Sclerosis	Parkinson's Disease
1	Technical feasibility and optimization	N/A†	N/A†	N/A†	N/A†	N/A†
2	Diagnostic accuracy	3 PET (47-49)	7 PET (50-56) 4 MRS (57-60) 1 PET + MRS (61)	4 PET (62-65) 5 fMRI (66-70) 8 MEG (71-78)	---	3 PET (79-81)
3	Diagnostic thinking impact	—	—	1 PET (82) 1fMRI (67) 1 MEG (83)	—	—
4	Therapeutic choice impact	1 PET (84)	1 fMRI (85)	—	—	—
5	Patient outcome impact	—	1 fMRI (86)	—	—	—
6	Societal impact	—	—	—	—	—

*fMRI indicates functional magnetic resonance imaging; MEG, magnetoencephalography; N/A, not applicable; PET, positron emission tomography.
†Level 1 studies of technical feasibility and optimization were not eligible for inclusion..

Results: Alzheimer's Disease

What is the role of functional brain imaging in the diagnosis of Alzheimer's disease?

There were no studies identified that met the inclusion criteria for this review that investigated the role of MEG, MRS or fMRI in the diagnosis of AD compared with a reference standard for diagnosis.

In 2003, Kulasingam et al. (84) developed a decision analysis regarding the use of PET in the diagnosis and management of AD. Their Markov-model-based decision analysis included asymptomatic men and women with a first-degree relative with AD or patients with mild dementia. The subjects were diagnosed based on the American Academy of Neurology (AAN) criteria alone or with PET and the AAN criteria. The AAN criteria consist of a complete history, physical and neuropsychological evaluations, and structural imaging tests (e.g., MRI or CT). Kulasingam et al. concluded that even though PET may provide a more accurate diagnosis than the AAN evaluation alone, there is not likely to be a clinical benefit of using PET. Their conclusion was based on the fact that cholinesterase inhibitors are the standard current medical management for AD, which is associated with few severe adverse events. Kulasingam et al. argued that if the most effective medical management for AD was associated with significant severe adverse events, then the use of PET may be more applicable in minimizing the number of false positive cases.

In a more recent publication, Kulasingam et al. (87) proposed a pragmatic trial of PET for AD; however, at this time, it does not appear that this trial has been initiated (personal communication, November 2, 2006).

Since the publication of the Agency for Health Research and Quality (AHRQ) health technology assessment in 2004, there were 3 additional studies (47-49) identified for this review confirming the accuracy of PET in the diagnosis of AD. However, none of these studies assessed whether the clinical outcomes for patients diagnosed with AD by PET are better than the outcomes for patients diagnosed by clinical evaluation. Table 8 describes the characteristics these studies.

Table 8: Characteristics of Studies of Functional Brain Imaging in the Diagnosis of Alzheimer's Disease*

Study	Type of Study	Imaging Modality	N	Description of Patients	Reference Standard	% Male	Mean (SD) Age, Years
Kawachi et al, 2006 (47)	Prospective cohort-control	FDG-PET	62 (60 healthy volunteers)	Very mild or mild AD	Clinical criteria (NINCDS/ADRDA), follow-up 1 year	27	67(5.8)
Dobert et al., 2005 (48)	Prospective cohort	FDG-PET, SPECT	24	Clinical suspicion of beginning dementia	Clinical follow-up 16 SD=12 months	46	69 (6.8)
Drzezga et al., 2005 (49)	Prospective cohort	FDG-PET	30	MCI	Clinical follow-up 16 SD=2 months	47	70 (8)

* AD indicates Alzheimer's disease; FDG, 18F-labelled-fluorodeoxyglucose; MCI, mild cognitive impairment; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography; SD, standard deviation; SPECT, single photon emission computed tomography.

Each of the studies used a different comparison with PET (MRI, SPECT, genetic assessment) (Table 9).

Also, as mentioned previously, none of these studies reported patient outcomes on the basis of the PET diagnosis. Consistent with the results of the AHRQ health technology assessment, the sensitivity and specificity of PET in these 3 studies was high (about 92% sensitivity and 89% specificity). From this it was concluded that despite diagnostic accuracy, evidence of clinical utility for PET in AD is lacking.

Table 9: Sensitivity and Specificity Reported in the Studies of Functional Brain Imaging for Alzheimer's Disease*

Study	Imaging Modality	N	Condition	Accuracy, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Kawachi et al., 2006 (47)	PET	30 + 60 healthy volunteers	Very mild AD	88.5	—	—	—	—
	VBM-MRI			82.9	—	—	—	—
Dobert et al., 2005 (48)	PET	24	Alzheimer's or mixed type of dementia	—	91.7	88.9	94.1	100
	SPECT			—	64.0	84.2	70.0	64
Drzezga et al., 2005 (49)	PET	30	MCI	90.0	92.0	89.0	85.0	94
	Genetic assessment (APOE genotype)			63.0	75.0	56.0	53.0	77

*AD indicates Alzheimer's disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon emission computed tomography; VBM, voxel-based morphology.

Results: Brain Tumours

There were 3 questions this review asked with respect to functional brain imaging for brain tumours:

➢ What is the role of functional brain imaging in the detection of primary tumours?
➢ What is the role of functional brain imaging in the differentiation of recurrence from radiation necrosis?
➢ What is the role of functional brain imaging in the selection of surgical candidates for tumour resection?

What is the Role of Functional Brain Imaging in the Detection of Primary Tumours?

In all of the studies identified that investigated the role of functional brain imaging in the detection of primary tumours, a suspicious lesion had already been identified; thus, the role of functional brain imaging was to determine if the lesion was benign or malignant. In most cases the reference standard was biopsy; however, in some cases, postoperative follow-up was used as the reference standard.

Six studies were identified that met the inclusion criteria for this review and that had been published since the most recent health technology assessments on functional brain imaging for brain tumours. Five investigated the role of PET using various radiotracers (18F-FDG, 18F-FLT, 11C-MET), and the other study investigated PET and MRS. Table 10 describes the characteristics of these studies. It is important to note that the half-lives for the radiotracers are variable, making some more appropriate for clinical practice than others. (Table 2 lists the half-lives of commonly used radiopharmaceuticals in PET scans)

Only the study by Pauleit et al. (52) blinded the clinicians from the patients' clinical histories. All of the studies established tumour diagnosis with biopsy or resection. Not all of the patients in all of the studies had suspected primary tumours, because there were patients in some of the studies who had been treated previously.

In the prospective study by Wang et al., (50) patients were included if they had positive but inconclusive MRI or CT results. The majority of patients in their study had brain metastases (n = 78) compared with primary brain tumours (n = 39); however, since they stratified the results for primary diagnoses and metastases, this study was eligible for inclusion.

Table 10: Characteristics of Studies Investigating the Detection and Grading of Primary Tumours With Functional Brain Imaging*

Study	Type of Study	Imaging Type	N	Type of Tumour	Blind	Reference Standard	Male, %	Mean Age, Years
Wang, 2006 (50)	PCS	18F-FDG-PET	117 (156 scans) 5 patients lost	39 primary tumours; 78 with metastases	No	Biopsy, resection, or clinical follow-up $\geq$ 2 years for primary tumours	50	52.9 (range, 7.9–81.4)
Choi, 2005 (51)	PCS	18F-FLT PET	26	26 with suspected tumours on MRI: 19 primary, 7 previously treated	No	23 biopsy (no time frame reported) 3 clinical follow-up	58	Median 34 (range, 2–67)
Jacobs, 2005 (53)	PCS	11C-MET PET 18F-FLT PET	23	Grade I=1; Grade II=8; Grade III=7 ; Grade IV=7; 15 treated; 8 untreated	No	Biopsy	48	47.1 (SD,14.6; range 20–70)
Pauleit, 2005 (52)	PCS	18F-FET PET	31 –3 patients exclude-ed	Grade I=2; Grade II=7; Grade III=12; Grade IV=2; Reactive astrogliosis= 5	Yes	Biopsy	32	42 (SD, 20)
Kracht, 2004 (54)	RS	11C-MET PET	30	22 primary; 8 suspected recurrence	No	Biopsy	47	40 (SD, 8.9)
Floeth, 2005 (61)	PCS	MRS and 18F-FET PET	91 had FET-PET (50 had MRS + FET PET)	Newly diagnosed glioma based on MRI	No	Biopsy	42	44.3, (range, 2–74; SD, NR)

* FDG indicates 18F-labelled-fluorodeoxyglucose; FET, O-(2[18]F-Fluoroethyl) –L-tyrosine; FLT, 18F-labelled-fluoro-3'-deoxyl-3'-L-fluorothymidine; MET, L-methyl-11C-methionine; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NR, not reported; PCS, prospective cohort study; PET, positron emission tomography; RS, retrospective study; SD, standard deviation.

The results of the studies investigating functional brain imaging for diagnosing malignant versus benign brain tumours are listed in Table 11. The thresholds defined by the studies are variable. The thresholds in the PET studies are ratios between normal tissue uptake of a radiotracer versus abnormal uptake. The thresholds in MRS studies are ratios between the metabolites.

Two of the studies relied on visual inspection to determine if a tumour was present, while all of the other studies defined quantitative thresholds. The threshold in the study by Wang et al. (50) was by visual inspection; however, they stated that if the FDG uptake in or near the lesion was lower than the surrounding tissue, the PET scan was considered to be negative. Alternatively, if the FDG uptake was higher in or near the lesion, the PET scan was considered positive. The study by Choi et al. (51) also made similar specifications for their visual inspection of images with FDG and FLT.

In all studies, most patients underwent MRI in addition to the MRS or PET scan. Only 2 of the studies compared the accuracy of MRS or PET and MRI, with MRI alone. (52;61) Gadolinium-enhanced MRI is the gold standard for the diagnosis of primary tumours (personal communication, clinical expert, November 15, 2006), thus a comparison to Gd-enhanced MRI is very worthwhile to establish if the results of the MRS or PET scans improve the accuracy of tumour diagnosis.

In the prospective study by Floeth et al., (61) patients with suspected primary tumours underwent MRI (Gd-enhanced), MRS, and FET-PET. Ninety-one patients received FET-PET; 50 of these also received a MRS analysis. Of the 50 patients undergoing PET, MRS, and MRI, 34 (68%) had malignant tumours confirmed after biopsies. Compared with MRS and FET-PET, Gd-enhanced MRI alone had lower sensitivity and specificity. Floeth et al. did not report if this difference in sensitivity and specificity was significant; however, they did report that by adding MRS and FET-PET to MRI the accuracy increased from 68% for MRI alone to 97% for MRS, FET-PET, and MRI. They did not report the accuracy of MRS and MRI without FET-PET, nor did they report the accuracy of FET-PET and MRI without MRS. There are some limitations of this study, including that the 2 neurosurgeons who reviewed the test results were not blinded, and that not all patients received the same intervention. It was unclear why some patients had MRS analyses and others did not.

The prospective study by Pauleit et al. (52) studied the use of FET-PET in 31 newly diagnosed patients with primary gliomas. They reported that compared with MRI (Gd-enhanced) alone, combining FET-PET with MRI (Gd-enhanced) resulted in a similar sensitivity (96% for MRI alone, 93% for FET-PET + MRI) and higher specificity (53% for MRI alone, 94% for FET-PET + MRI) for tumour diagnosis. The 3 observers who reviewed the results were blinded to the clinical information of the patients included in the study. Twenty (71%) of 28 patients analyzed (3 patients were excluded from the analysis) had malignant tumours confirmed by biopsies.

Table 11: Results of Studies Investigating Functional Brain Imaging for Diagnosing Malignant Versus Benign Lesions*

Study	Imaging Type	Type of Tumour	Malignant/ Benign Diagnoses Confirmed by Biopsy	Threshold	Sensitivity, %	Specificity, %
Wang et al., 2006 (50)†	18F-FDG PET	Primary	Of 17 patients with biopsy results: 10/7	Visual inspection	76	96
Choi et al., 2005 (51)	18F-FLT PET	Primary and recurrent	18/8	Visual inspection	79	63
Jacobs et al., 2005 (53)	11C-MET PET	Primary	23/0	1.3	91	All patients had tumour
	18F-FLT PET			2.0	78	
Pauleit et al., 2005 (52)‡	18F-FET PET	Primary	20/8	1.6	93	94
	MRI (Gd enhanced, T1)			0.9	96	53
Kracht et al., 2004 (54)	11C-MET PET	Primary and recurrent	24/6	1.3	87	89

Study	Imaging Type	Type of Tumour	Malignant/ Benign Diagnoses Confirmed by Biopsy	Threshold	Sensitivity, %	Specificity, %
Floeth et al., 2005 (61)	MRS	Primary	34/16	NAA/Cho 0.7 Low or absence of NAA or high Cho indicative of tumour	100	81
	18F-FET PET			tumour/brain tissue ratio 1.6	88	88
	MRI (Gd-enhanced, T1)			NR	44	69

*Cho indicates choline; FDG, 18F-labelled-fluorodeoxyglucose; FET, O-(2[18]F-Fluoroethyl)-L-tyrosine; FLT, 18F-labelled-fluoro-3'-deoxyl-3'-L-fluorothymidine; Gd, gadolinium; MET, L-methyl-11C-methionine; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyaspartate; NR, not reported; PET, positron emission tomography.

† Wang et al. (50) also reported that there were 13 cases which were indeterminate on PET scans, thus did not make a diagnosis and were not included in the accuracy calculations.

‡ In the study by Pauleit, the 3 readers used a 6-point scale to establish presence or absence of a brain tumour. The scale was as follows: 6, definitely positive; 5, probably positive; 4, possible positive; 3, possibly negative; 2, probably negative; 1, definitely negative for tumour tissue. For the determination of sensitivity and specificity, a score greater than or equal to 4 was considered positive for tumour tissue.

Table 12 groups the results for sensitivity and specificity by imaging modality and radiotracer and threshold. In both 11C-MET PET and 18F-FET PET, sensitivities and specificities are consistently high.

Table 12: Sensitivity and Specificity for Functional Brain Imaging for the Diagnosis of Brain Tumours*

Accuracy	18F-FDG PET	18F-FLT PET	18F-FLT PET	11C-MET PET	18F-FET PET	MRS
Threshold	Visual inspection	Visual inspection	2.0	1.3	1.6	NAA/Cho 0.7 Low or absence of NAA or high Cho indicative of tumour
Sensitivity	76%	79%	78%	91% 87%	93% 92% 88% 94%	100%
Specificity	96%	63%	—	— 89%	81% 88%	81%

*Cho indicates choline; FDG, 18F-labelled-fluorodeoxyglucose; FET, O-(2[18]F-Fluoroethyl)-L -tyrosine; FLT, 18F-labelled-fluoro-3'-deoxyl-3'-L-fluorothymidine; MET, L-methyl-11C-methionine; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; PET, positron emission tomography.

Unfortunately, none of these authors commented on whether the accurate diagnosis of brain tumours had an impact on treatment or clinical outcomes in the patients in these studies. Patients with primary tumours are likely to have biopsies despite imaging results (personal communication, clinical expert, December 5, 2006).

What is the Role of Functional Brain Imaging in the Differentiation of Recurrence From Radiation Necrosis?

There were 6 studies identified since the most recent health technology assessments were published that examined the use of functional brain imaging in the differentiation of recurrence and radiation necrosis (3 RS' and 3 prospective studies). Four used MRS and the other 2 used PET (18F-FDG, 18F-FDOPA and 18F-FET). Table 13 describes the characteristics of the studies.

Table 13: Characteristics of Studies Investigating the Differentiation of Recurrence From Radiation Necrosis Using Functional Brain Imaging*

Study	Type of Study	Imaging Type	N	Type of Tumour	Duration Since Treatment for Primary Diagnosis, Months	Blinded	Ref. Standard	Male, %	Mean Age, Years
Chen et al., 2006 (55)	PCS	18F-FDOPA PET 18F-FDG PET	30	11 primary 70 previously treated Only 30 patients underwent PET scans	NR	No	15 patients biopsy within 3 wks 15 patients clinical follow-up, mean 20 mths	60	45.2 (SD, 14; range, 23–68)
Sundgren et al., 2006 (58)	RS	MRS	28	Previously treated brain tumours (various)	Mean, 23 (range, 6–56)	Yes	Biopsy, surgery, clinical follow-up	54	35 (range, 5–56)
Rachinger et al., 2005 (56)	RS	18F-FET PET	45	Previously treated brain tumours (various)	NR	No	27 biopsy 5 resection 13 clinical follow-up	51	45 (SD, 12; range, 26–75)
Palumbo et al., 2006 (60)	RS	MRS	30 glioma patients - operated on and treated with RT	Previously treated brain tumours (various)	6–12	No	Biopsy/ resection	73	53.5 (SD, 14; range, 25–76)
Lichy et al., 2005 (57)	RS	MRS	34 (23 included in analysis)	Previously treated brain tumours (various)	37 (SD, 12 months)	Yes	Biopsy/ resection	65	Median, 45 (range, 18–70)
Weybright et al., 2005 (59)	PCS (cones-cutive)	MRS	29 (28 in analysis)	Previously treated brain tumours (various)	2–108 months	No	Biopsy/ resection	55	34 (range, 4–54)

*FDG indicates 18F-labelled-fluorodeoxyglucose; FDOPA, fluorodopa ; FET, O-(2^{18}F-Fluoroethyl)-$_L$-tyrosine; MRS, magnetic resonance spectroscopy; NR, not reported; PCS, prospective cohort study; PET, positron emission tomography; RS, retrospective study; RT, radiation therapy; SD, standard deviation.

Table 14 outlines the results reported by each of the 6 studies identified that used MRS or PET to differentiate recurrence from radiation necrosis. Similar to the studies identifying primary brain tumours, various thresholds were used to determine presence of recurrence.

The study by Rachinger et al. (56) compared FET-PET with MRI (with and without Gd enhancement) to MRI alone in 45 patients with suspected tumour recurrence. They found that MRI with FET-PET had higher specificity than MRI alone (93% versus 50%, respectively). Sensitivity was also higher for PET

with MRI versus MRI alone (100% versus 94%). Rachinger et al. reported that the difference in accuracy between PET and MRI versus MRI alone was significant ($P \leq .05$). It is unclear whether the reviewers of the PET and MRI results were blinded to the patients' clinical information.

The study by Lichy et al. (57) was the only study identified that compared MRS with Gd-enhanced MRI to Gd-enhanced MRI alone. They reported the highest sensitivity and specificity when MRS was combined with T1 (Gd-enhanced) and T2 MRI (100% and 86%, respectively); however, T1 and T2 MRI also had high sensitivity and specificity without MRS (94% and 86%, respectively). It is unclear if the added benefit of MRS in terms of sensitivity is significant.

The sensitivity and specificity in the study by Sundgren et al. (58) were calculated by the Medical Advisory Secretariat using the following assumptions:

➢ True positive: Patients with recurrence on MRS confirmed through clinical, neuroradiologic or neuropathologic follow-up.
➢ True negative: Patients with radiation injury on MRS confirmed through clinical, neuroradiologic or neuropathologic follow-up.
➢ False positive: Patients with recurrence or inconclusive results on MRS but radiation injury confirmed through clinical, neuroradiologic or neuropathologic follow-up.
➢ False negative: Patients with radiation injury on MRS but recurrence confirmed through clinical, neuroradiologic or neuropathologic follow-up.

Based on these assumptions, the sensitivity and specificity for MRS in this study were 88% and 70%, respectively.

Table 14: Results of Studies Investigating Functional Brain Imaging for Brain Tumours*

Study	Imaging Type	Type of Tumour	Recurrence / Benign Diagnosis Based on Biopsy	Threshold	Sensitivity, %	Specificity, %
Chen, 2006 (55)	18F-FDOPA PET	Primary and recurrent	23/7	Visual inspection	96	43
	18F-FDG PET				61	43
Rachinger, 2005 (56)	18F-FET PET	Various	31/14	2.2	100	93
	MRI (Gd enhanced)			≥ 25% increase in tumour	94	50
Palumbo, 2006 (60)	MRS	Various	20/10	Cho/Cr 2.0	90	100
	SPECT			NR	90	83
Sundgren et al., 2006 (58)†	MRS	Various	18/10	Cho/Cr 1.8 Cho/NAA 1.8 (same results for both ratios)	‡88	‡70
Lichy et al., 2005 (57)	MRS	Various	16/7	Cho/Cr 2.0	81	71
	MRI T1-Gd-enhanced			≥ 25% increase in tumour	81	57
	MRI T1 -Gd-enhanced + T2				94	86
	MRS + MRI T1 GD-enhanced +T2				100	86
Weybright et al., 2005 (59) †	MRS	Various	16/12	Cho/Cr 1.8 Cho/NAA 1.8 (same results for both ratios)	94	100

Table 15 groups the results for sensitivity and specificity by imaging modality and radiotracer and threshold. Both of the studies by Palumbo et al. (60) and Lichy et al. (57) reported accuracy for MRS using the Cho/Cr ratio threshold of 2.0. The study by Palumbo et al. reported a higher specificity than sensitivity (90% sensitivity, 100% specificity) while the study by Lichy et al. reported a higher sensitivity than specificity (81% sensitivity, 71% specificity). The study by Weybright et al. (59) also reported accuracy of MRS using Cho/Cr ratio; however, they used a different threshold (1.8), but they reported similar results to Palumbo et al. (94% sensitivity and 100% specificity).

Rachinger et al. reported the highest sensitivity (100%) using 18F-FET-PET. The highest specificity (100%) was reported by Palumbo et al. and by Weybright et al. for MRS using the Cho/Cr ratio.

As in those studies that investigated the use of PET and MRS in patients with primary tumours, none of these studies reported how the accuracy of diagnosis had an impact on treatment or clinical outcomes.

Table 15: Sensitivity and Specificity for Functional Brain Imaging for the Diagnosis of Brain Tumours*

Accuracy	18F-FDG PET	18F-FET PET	18F-FDOPA	MRI T1 + T2	MRS	MRS	SPECT
Threshold	Visual inspection	2.2	Visual inspection	≥25% increase in tumour	Cho/Cr 1.8 or Cho/NAA	Cho/Cr 2.0	NR
Sensitivity %	61	100	96	94 94	94 †88	90 81	90
Specificity %	43	93	43	50 86	100 †70	100 71	83

* Cho indicates choline; Cr, creatine; 18F-FDG, 18F-labelled-fluorodeoxyglucose; FDOPA, fluorodopa;18F-FET, O-(2-^{18}F-Fluoroethyl)-$_L$-tyrosine; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; NR, not reported; PET, positron emission tomography; SPECT, single photon emission computed tomography; T1, gadolinium enhanced.
†Medical Advisory Secretariat Calculation

What is the Role of Functional Brain Imaging in the Selection of Surgical Candidates for Tumour Resection?

There is considerable evidence indicating that fMRI and MEG can accurately identify the sensorimotor complex; (88-97) however, the impact of this on surgical outcomes is not reported in the studies identified. The role of fMRI is to identify the language, sensory, and motor areas of the brain, with the aim of establishing whether tumour resection will affect language, sensory, or motor function. The primary purpose of fMRI is not to identify tumours, as it is with PET and MRS.

One study, by Ganslandt et al., (98) reported on surgical outcome after fMRI or MEG, but did not provide a comparison of what the surgical outcome would have been without fMRI or MEG.

Two studies (85;86) were identified that described the role of functional brain imaging in the selection of surgical candidates for tumour resection. Both investigated the role of fMRI in the selection of patients for surgery.

The case-control study by Winkler et al. (86) compared surgical outcomes in patients with brain tumours who had preoperative imaging with fMRI (n = 49) with those who underwent surgery without preoperative fMRI (historical controls, n = 55). In both groups there were patients with meningiomas (18 in experimental group, 19 in control group), metastases (9 in experimental group, 19 in control group), and stage II to IV gliomas (22 in experimental group, 17 in control group). The mean age of the patients was 53.9 years (range, 14–78 years) in the experimental group, and 52.3 years (range 21–76 years) in the control group.

At 6 months postoperatively, patients were categorized as "improved," "unchanged," or "deteriorated" in terms of neurological function; tumour outcome results were not reported. Table 16 outlines the results. Winkler et al. reported the results separately for the various tumour types.

There appears to be more inconsistency across outcomes in the patients with gliomas compared with the patients with metastases or meningiomas. However, Winkler et al. reported that there were no statistically significant differences in neurological function outcomes between patients who had undergone preoperative fMRI and those who had not. However, due to small sample subsets the study may not have been powered to detect a significant difference in outcomes (Type II error).

Table 16: Outcomes of Patients With Preoperative Functional Magnetic Resonance Imaging Versus Without Preoperative Functional Magnetic Resonance Imaging 6 Months Postoperatively*

Tumour Type	Unchanged		Improved		Deteriorated	
	Preop fMRI (%)	Control (%)	Preop fMRI (%)	Control (%)	Preop fMRI (%)	Control (%)
Meningiomas (n = 37)	14 (78)	13 (68)	2 (11)	4 (21)	2 (11)	2 (11)
Metastases (n = 28)	6 (67)	12 (63)	2 (22)	3 (16)	1 (11)	4 (21)
Gliomas (n = 39)	15 (68)	5 (29)	2 (9)	5 (29)	5 (23)	7 (40)
Total (N = 104)	35 (71)	30 (55)	6 (12)	12 (22)	8 (16)	13 (24)

*fMRI indicates functional magnetic resonance imaging.

Source: Winkler D, Strauss G, Lindner D, Richter A, Georgiadis MH, Von Cramon Y et al. The importance of functional magnetic resonance imaging in neurosurgical treatment of tumors in the central region. Klinische Neuroradiologie 2005; 15:182–189

This study suffered from several limitations. There was no blinding, nor was there a sample size calculation reported explaining how the authors chose their sample size. There was also limited information regarding eligibility criteria and whether the patients were enrolled consecutively. Nonetheless, this was the only study identified that compared outcomes after surgery based on fMRI.

In the prospective cohort study by Petrella et al., (85) 39 patients with potentially resectable tumours were imaged preoperatively with fMRI. Three neurosurgeons completed a questionnaire regarding the treatment plan for the patients before and after seeing the fMRI results. Petrella et al. did not report what clinical information was provided to the neurosurgeons before the fMRI to develop treatment plans. It is important to note that the role of fMRI is to identify the sensorimotor cortex, not to identify tumours. Table 17 describes the neurosurgeons' responses before and after fMRI.

Before fMRI the neurosurgeons thought that 9 patients were not suitable for any surgical intervention. After fMRI, the treatment plan for 7 of the 9 patients changed (2 biopsy, 5 craniotomy with mapping). All of the 8 patients who had a biopsy as their treatment plan before fMRI had their treatment plan changed after fMRI. All 8 patients were changed to craniotomy (7 with intraoperative mapping, 1 under general

anesthesia). Overall, the treatment plan was altered in 19 of 39 patients (49%; 95% CI, 33%–64%), with 18 of the 19 treatment plans being more aggressive after fMRI.

In addition to the treatment plan, 4 patients also had Wada tests recommended prior to fMRI. After fMRI none of the patients required this invasive test.

It was the clinical impression of the neurosurgeons in the study by Petrella et al. that fMRI shortened surgical time by an estimated 15 to 60 minutes in 60% of patients. However, they did not report how this was calculated.

There is no long-term follow-up reported for the patients in the study by Petrella et al. (85) The authors reported that the "[a]ctual intervention agreed with the treatment plan after functional MR imaging in all 39 patients."

Table 17: Responses of Neurosurgeons Before and After Functional Magnetic Resonance Imaging Results Were Analyzed*

Surgical Options	Treatment Plan After fMRI			
Treatment Plan BEFORE fMRI	No Surgery	Biopsy	Craniotomy With Intraoperative Mapping	Craniotomy With General Anesthesia
No surgery	2	2	5	0
Biopsy	0	0	7	1
Craniotomy without general anesthesia	0	1	13	3
Craniotomy with general anesthesia	0	0	0	5

*fMRI indicates functional magnetic resonance imaging
Reprinted with permission from the Radiological Society of North America and the author; Petrella JR, Shah LM, Harris KM, Friedman AH, George TM, Sampson JH et al. Preoperative functional MR imaging localization of language and motor areas: Effect on therapeutic decision making in patients with potentially resectable brain tumors. Radiology 2006; 240:793–80.2

In summary, fMRI and MEG can accurately identify the sensorimotor cortex, as has been demonstrated in several studies. According to the study by Winkler et al., (86) there is no difference in surgical outcome in patients who have had preoperative fMRI compared with those who have not. However, this was a low-quality study that may not have been powered to detect a significant difference between groups. The study from Petrella et al. (85) demonstrated that the treatment plan for patients changed with the information provided with preoperative fMRI results and that preoperative fMRI may also decrease surgery time.

Results: Epilepsy

What is the Role of Functional Brain Imaging in the Localization of Seizure Foci?

As described earlier in this review, the current gold standard for localizing seizure foci includes video scalp EEG (which is noninvasive, but time consuming, usually involving taking patients off their medications and several days in hospital), MRI, and neuropsychological evaluation. If the results are inconclusive, then invasive ICEEG is considered. The literature has identified 2 possible roles for functional brain imaging in localizing seizure foci:

➢ an imaging test to be used instead of or in addition to noninvasive EEG, and
➢ an imaging test to replace ICEEG.

Functional Brain Imaging Versus Intracranial Electroencephalogram

Intracranial electroencephalogram is the gold standard for localizing seizure foci in patients with inconclusive noninvasive results. Based on 3 studies (described in the Alternative Technologies section of this review), (26;27;99) the range of surgical success (seizure-free or significant improvement in seizures) based on ICEEG is from 57% to 89%.

There were 3 studies identified that investigated the localization of seizure foci with MEG compared with ICEEG. An additional 3 studies from the Blue Cross Blue Shield health technology assessment (43) are also described below to enhance the results of the newly identified studies. In addition, since the Blue Cross and Blue Shield health technology assessment reported that due to insufficient evidence they could not recommend using MEG, the Medical Advisory Secretariat wanted to further investigate previous MEG studies in order to draw some conclusions from the results of the studies on MEG. The Medical Advisory Secretariat extracted the 3 studies from the Blue Cross Blue Shield health technology assessment that included 20 or more patients and compared MEG to ICEEG relative to surgical outcomes. There were no studies identified comparing other functional brain imaging modalities besides MEG to ICEEG. Table 18 describes the characteristics of these studies.

Table 18: Characteristics of Studies Investigating the Localization of Seizure Foci With Functional Brain Imaging Instead of Intracranial Electroencephalogram*

Study	Type of Study	N	Description of Patients	Seizure Origin	Blind	Reference Standard	% Male	Mean Age (Range), Years
Knowlton et al., 2006 (71)	Prospective	49	Patients with intractable partial epilepsy	ETLE—21 MTLE—18 LTLE—6 Nonlocal-ized—4	No	ICEEG and/or early surgical outcome	55	27 (1–61)
Oishi et al., 2006 (78)	Retrospective	20	Medically refractory Neocortical epilepsy	Various	No	Seizure outcome postoperatively (1 year follow-up)	65	26.5 (7–52)
Papanicolaou et al., 2005 (75)	Retrospective	41	Patients with epilepsy who had undergone surgery	TLE—29 ETLE—12	Yes	Seizure outcome postoperatively (1 year follow-up)	54	27.4 (7–54)
Mamelak et al., 2002 (100)	Prospective	40 (23 under-went ICEEG)	Patients with suspected focal epilepsy,		Yes	Seizure outcome postoperatively (mean 21 months follow-		

Study	Type of Study	N	Description of Patients	Seizure Origin	Blind	Reference Standard	% Male	Mean Age (Range), Years
			refractory			up (range 13–32))		
Wheless et al., 1999 (101)	Prospective	58	Patients with refractory partial epilepsy	TLE—35 ETLE—17 Mixed—6	Yes	Seizure outcome (range 6–46 months, 85% of patients had > 12 months follow-up)	48	26.7 (7–55)
Gallen et al., 1997 (102)	Prospective	33	Patients with intractable epilepsy being considered for surgery	TLE—27 ETLE—6	Yes	Seizure outcome postoperatively (> 2 years follow-up)	61	34 (14–58)

* ETLE refers to extratemporal lobe epilepsy; ICEEG, intracranial electroencephalogram; LTLE, lateral temporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy.

The PCS by Knowlton et al. (71) was designed to address whether MEG can replace ICEEG in the presurgical evaluation of patients with refractory epilepsy. This study has clinical relevance because it compared MEG to ICEEG, the current gold standard. When MEG was compared with ICEEG and surgical outcome, the values for sensitivity and specificity were 75% and 70%, respectively. They also reported subgroup analyses, the results of which suggested that MEG may be less beneficial compared with ICEEG in patients with extratemporal lobe epilepsy (ETLE) compared with those with temporal lobe epilepsy (TLE). This result was based on a subset analysis, and the study was not designed to compare differences between ETLE and TLE.

Knowlton et al. (71) concluded that MEG could potentially replace the invasive ICEEG. However, there were 2 letters to editor (103;104) regarding this study which stated that the results by Knowlton et al. are promising, but must be considered with caution for the following reasons:

➢ Knowlton et al. (71) did not clearly differentiate neocortical from temporolimbic epilepsy (although the inclusion criteria would have limited the number of patients with bilateral temporolimbic epilepsy).
➢ For patients with temporolimbic epilepsy, the need to identify the intracranial epileptic (ictal) onsets is more important than the identification of interictal spikes captured by MEG, thus MEG does not aid in the surgical planning of patients with temporolimbic epilepsy.
➢ Potential for bias in favour of MEG, in cases where resection success was primarily due to ICEEG but included MEG dipoles in the planned resection area.
➢ In 7 of 49 (14%), cases were localized by ICEEG, but not MEG. Three (6%) cases were localized by MEG, but not by ICEEG.

The small retrospective study by Oishi et al. (78) compared MEG to ICEEG in 20 patients with medically refractory neocortical epilepsy. Based on postoperative outcomes using Engel's classification, (105) they reported that MEG results were significantly correlated with surgical outcomes in patients in which MEG detected single clusters compared with patients in which MEG detected multiple clusters ($P = .049$). Patients with single clusters were more likely to be seizure-free after surgery than patients with multiple clusters detected on MEG. There was also a significant correlation between the results for MEG and ICEEG ($P = .014$). However, it is important to note that patients with multiple foci are less likely to benefit from surgical resection compared with patients with localized foci.

In the prospective study by Gallen et al., (102) 33 patients underwent presurgical evaluation for the resection of seizure foci. After the presurgical evaluation, 4 patients were considered inappropriate surgical candidates. Of the remaining 29, 21 (72%) were seizure-free at a mean follow-up of 42.4 months (standard deviation [SD], 8.9 months; range 25–57 months). Twenty-one patients required ICEEG monitoring prior to surgery. They reported on sensitivity and specificity for MEG, ICEEG, noninvasive EEG (video monitoring), neuropsychological testing, and MRI. They reported higher sensitivity and specificity for ICEEG compared with all the other modalities, including MEG.

The retrospective study by Papanicolaou et al. (75) compared ICEEG to MEG in 41 patients with refractory epilepsy. Surgical focal resection was based on the results of the ICEEG, MRI, neuropsychological evaluation, SPECT, PET, and Wada testing. Magnetoencephalography and ICEEG results were compared with postoperative outcomes (using the Wieser classification (106)). Compared with postoperative outcomes, MEG was correct in 23 (56%) of 41 patients, and ICEEG was correct in 22 (54%) of 41 patients. Predictions were incorrect for 15 patients with MEG and 16 patients with ICEEG, and there were 3 indeterminate cases for each MEG and EEG.

All 5 of the studies reported concordance or agreement with the resected area for both MEG and ICEEG. In all of the studies, the decision as to where to resect was based on a multitude of tests, including MRI, noninvasive EEG, neuropsychological testing, and ICEEG. Some patients also underwent PET, SPECT, and/or Wada testing. Only in the study by Knowlton et al. could the MEG results impact the decision as to where to resect; however, MEG could only add to increase the selected area, it could not change the area to resect. Table 19 summarizes the agreement of MEG and ICEEG to the actual resected area.

Based on the results of these studies, the agreement between MEG and the resected area ranged from 49% to 71%, and the agreement between ICEEG and the actual resected area ranged from 44% to 74%. It is important to note that 4 of the 5 studies reported that the rate of agreement between ICEEG and the resected area was between 68% and 74%. The study by Wheless et al. (101) reported an agreement of only 44% for ICEEG. It is unclear why agreement was lower in this study compared with the others. If this study were removed, the range for MEG would remain the same (49%–71%) and the range for ICEEG would be improved (68%–74%).

Table 19: Agreement Between Resected Area and Magnetoencephalography and Intracranial Electroencephalogram*

Study	Agreement With Resected Area, %		Partial Agreement With Resected Area, %		No Agreement With Resected Area, %	
	MEG	Invasive EEG	MEG	Invasive EEG	MEG	Invasive EEG
Knowlton et al., 2006 (71)	65	69	14	20	21	11
Papanicolaou et al., 2005 (75)	71	68	19	24	10	8
Mamelak et al., 2002 (100)	57	74	43	26	—	—
Wheless et al., 1999 (101)	52	44	23	23	25	32
Gallen et al., 1997 (102)	49	71	15	24	36	5
Range	49–71	44–74	14–43	20–26	10–36	5–32

*EEG indicates electroencephalogram; MEG, magnetoencephalography.

In addition to the studies identified that described the accuracy of MEG in identifying the epileptic foci compared with ICEEG or noninvasive EEG, the retrospective study by Stefan et al. (83) investigated the clinical use of MEG results. They reported on 455 patients who underwent MEG for refractory epilepsy. As part of this review, 2 expert clinicians reviewed the 104 patients' charts and rated the contribution of the MEG results compared with other modalities used to localize the epileptic foci (video EEG, MRI, SPECT, MRI, etc.). The results were as follows:

➢ Disagreement between MEG and other modalities: 2 (2%) patients
➢ MEG results made no contribution: 10 (10%) patients
➢ MEG results in agreement with other modalities: 56 (54%) patients
➢ MEG provided additional information: 25 (24%) patients
➢ MEG had influence on surgical procedures: 11 (11%) patients

Based on the results of MEG compared with ICEEG and noninvasive EEG, it is difficult to draw conclusions regarding the effectiveness of MEG due to limitations in the evidence. The studies identified are mostly small case-series with heterogeneous samples. The patients in the studies have variable types of epilepsy, ages, duration of seizures, location of seizures, and variable presurgical evaluations. Moreover, the study designs and outcomes reported vary across studies.

Functional Brain Imaging Versus Noninvasive Electroencephalogram

There were 8 studies identified that investigated the localization of seizure foci with MEG or PET instead of or in addition to noninvasive (scalp) EEG. The characteristics of the studies are described in Table 20. Four of the studies compared MEG to EEG, and 4 compared PET to EEG. The 4 studies investigating the role of PET in the localization of seizure foci were conducted by the same core group of authors; thus, there may be overlap in the patients included in these studies. Patients were heterogeneous across the studies on several variables including age and seizure origin.

Table 20: Characteristics of Studies Investigating the Localization of Seizure Foci With Functional Brain Imaging Instead of Noninvasive (Scalp) Electroencephalogram*

Study	Imaging Type	N	Description of Patients	Blind	Male, %	Mean Age, Years
Yun et al., 2006 (62)† Retrospective	PET	193	Neocortical, intractable epilepsy (61 FLE, 80 nTLE, 21 PLE, 22 OLE, 9 multifocal)	Yes	66 seizure-free 65 persistent seizure	Seizure-free: 26.4 (SD, 7.5) Persistent seizure 27.0 (SD, 8.4)
Iwasaki et al., 2005 (73) Retrospective	MEG	43	Intractable focal epilepsy (36 TLE, 3 FLE, 2 FTLE, 2 PLE)	Yes	58	26.0 (range, 5–47)
Lee et al., 2005 (63)† Retrospective	PET	89	Neocortical, intractable epilepsy with normal MRI results (35 FLE, 31 nTLE, 11 PLE, 11 OLE, 1 multifocal)	Yes	62	25.6 (SD, 7.9; range, 8–56
Lee et al., 2005 (64)† Retrospective	PET	26	Neocortical, intractable epilepsy with normal MRI results	Yes	62	25.9 (SD, 7.6; range, 14–44)

Study	Imaging Type	N	Description of Patients	Blind	Male, %	Mean Age, Years
			(26 OLE)			
Ochi et al., 2005 (72) Retrospective	MEG	41	Intractable localization-related epilepsy	No	37	8.9 (range, 5 months –16 years)
Assaf et al., 2004 (74) Prospective	MEG	26	Intractable TLE	Yes	NR	NR
Kim et al., 2004 (65)† Retrospective	PET	40	Neocortical, intractable epilepsy (40 PLE)	Yes	53	27.0 (SD, 6.9 ; range, 12–40)
Pataraia et al., 2004 (77) Prospective	MEG	113 (results for 82 patients)	Drug-resistant epilepsy (54 TLE, 28 ETLE)	No	50	25.3 (range, 1.2–54)

* ETLE refers to extratemporal lobe epilepsy; FLE, frontal lobe epilepsy; FTLE, frontotemporal lobe epilepsy; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; NR, not reported; nTLE, neocortical temporal lobe epilepsy; OLE, occipital lobe epilepsy; PET, positron emission tomography; PLE, parietal lobe epilepsy; SD, standard deviation; TLE, temporal lobe epilepsy.
†There is likely overlap in the patients included in the studies by Yun et al., 2006, (62) Lee et al., 2005, (63) Lee et al., 2005 (64) and Kim et al., 2004. (65)

Due to the heterogeneity of the studies in the sample population, study design, and methods for reporting outcomes, the results of the studies could not be pooled. The results of the studies are described below.

The retrospective study by Iwasaki et al. (73) compared the results of simultaneous noninvasive EEG and MEG recordings in 43 patients with intractable focal epilepsy. Patients underwent focal resection based on an independent diagnosis not related to the study. Three expert reviewers were blinded to the clinical information of patients.

In 31 patients, spikes were detected in both MEG and EEG; in 8 patients, spikes were only detected with MEG, and in 1 patient spikes were detected by EEG alone. There were 3 patients who did not have any spikes detected with either modality. The authors did not report if one modality was better at identifying spikes in certain locations. Iwasaki et al. reported that there was not a significant difference in the total number of spikes detected by MEG compared with EEG ($P = .81$). Thirty-five of 43 patients were reported to be seizure-free postoperatively. Of these patients, MEG detected interictal spikes in 32 (91%) compared with 27 (77%) patients with EEG alone. In the 32 patients with MEG spikes detected, 25 (78.1%) were localized to the resection site. In the 27 patients with EEG spikes detected, 23 (85.2%) were localized to the resection site.

The retrospective study by Ochi et al. (72) compared the concordance between lateralization of MEG and noninvasive EEG with video monitoring in 41 children. They found there was concordance between MEG and EEG in 34 patients (83%). None of the patients with nonconcordant results underwent surgery.

In the prospective study by Assaf et al., (74) video scalp EEG recordings were compared with MEG results in 26 patients with intractable TLE. Twenty-two patients underwent surgery. The surgeons were blinded to the MEG results. Surgical decisions were based on scalp EEG recordings, in addition to other presurgical analyses (MRI, neuropsychological testing), in 15 patients. The other 7 patients who had surgery also had ICEEG in addition to the video scalp EEG and other presurgical tests. The authors reported statistically significant correlation between MEG and surgical resections ($P < .001$). Twenty-one of the 22 patients who underwent surgery were seizure-free postoperatively (duration of follow-up was not reported).

The prospective study by Pataraia et al. (77) compared MEG to noninvasive video EEG. They included 113 patients with refractory epilepsy in their study, but they only reported results for 82 patients. Sixteen patients were excluded due to large magnetic artifacts in their MEG results, and another 15 patients were excluded because their results were damaged in a flood. The decision to undergo surgery was based on video EEG, MRI, neuropsychological evaluation, SPECT, PET and Wada testing. The MEG results were not considered in the surgical decision. Both the MEG and the video EEG results were compared with the actual resected region. There was agreement between MEG and EEG in 32.3% of cases. Seventeen patients (20.7%) had no spikes on MEG, and were excluded from the analysis. There was perfect overlap for MEG in 47 of 65 patients compared to the actual resected area and 26 of 65 patients with EEG. There were 5 patients where they had partial overlap or no overlap in MEG, but perfect overlap in EEG. Alternatively, there were 26 patients with partial overlap or were nonlocalizable in EEG, but had perfect overlap in MEG.

Pataraia et al. reported 1-year postoperative outcomes for the patients in their study based on the Wieser classification. (106) A Wieser classification of 1 or 2 (no seizures or only aura) was considered to be success. A Wieser classification between 3 and 4 indicates that the patient has had a worthwhile improvement from seizures, and a classification of 5 indicates that there has been no or minimal improvement in the frequency of seizures. Based on data provided in the Pataraia et al. study, the Medical Advisory Secretariat created Figures 1 and 2 to illustrate the postsurgical outcome based on MEG and video EEG results. Of the 43 patients that were seizure-free 1 year after surgery, MEG localized the resected area in 25 patients (58%), compared with 42% for EEG. However, for the 19 patients who experienced no or minimal improvement in seizures after 1 year, MEG agreed with the resected area in 63% of cases, compared with 32% for EEG. Based on these results, it would appear that MEG has a higher sensitivity than video EEG, but a lower specificity. Pataraia et al. concluded that MEG may have a role in cases where video EEG is partially or nonlocalizing.

Figure 1: Magnetoencephalography Results Compared With 1-Year Postoperative Outcome (Based on Wieser Classification)
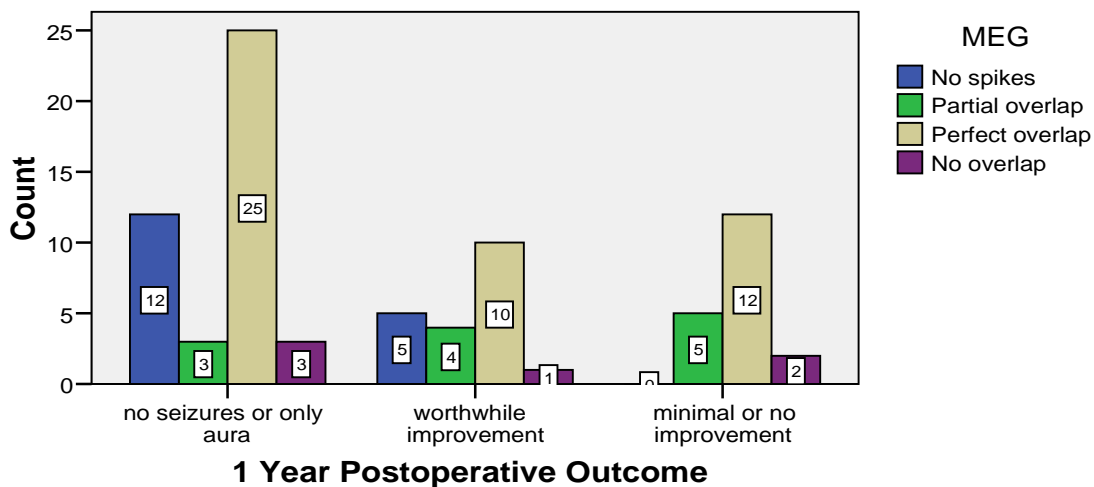
Figure 2: Noninvasive Video-Electroencephalogram Results Compared With 1-Year Postoperative Outcome (Based on Wieser Classification)
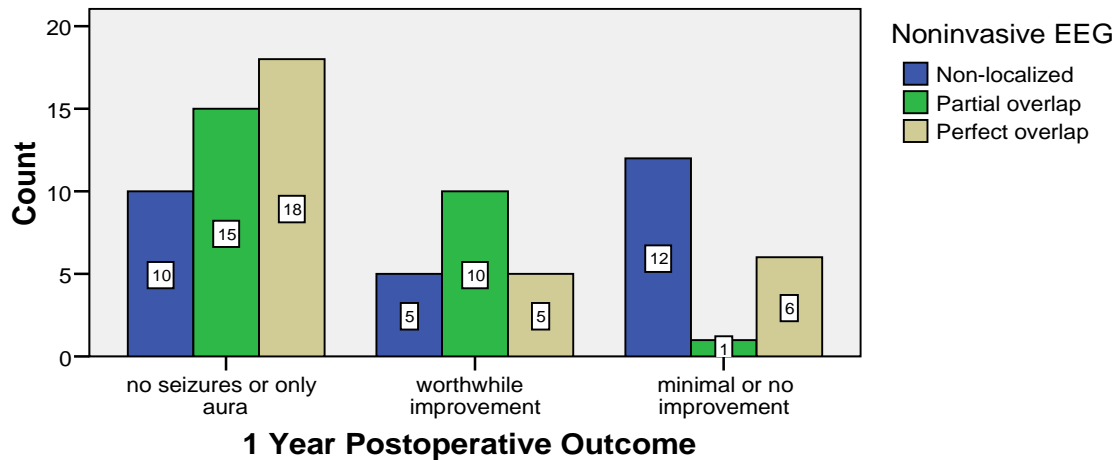
Since the publication of the NHS health technology assessment on PET in patients with epilepsy, 4 studies were identified that investigated the accuracy of PET in patients with epilepsy. (62-65) These 4 studies were conducted by the same core group of authors, thus there is likely overlap in the patients in the studies.

Table 21 outlines the percentage of accurate localizations of seizure foci by imaging modality. Accuracy was based the imaging modality localizing the resected area and on patients being seizure-free 1 year postoperatively. Across the 4 studies, there was variability in the sample size and type of epilepsy that was included. Single photon emission computed tomography appeared to be the least accurate, however, when observing the ranges covered by each of the modalities in the 4 studies, there was overlap across all modalities in terms of accuracy rates. Thus, it is not possible to conclude that 1 modality is better than another at localizing seizure foci based on these 4 studies.

Table 21: Percentage of Accurate Localizations by Modality (Based on 1-year Postoperative Outcomes)*

| Studies | % Localized by Imaging Modality & Seizure-Free $\geq$ 1 yr Postoperatively | | | |
	PET	Noninvasive EEG	Noninvasive EEG During Seizure	SPECT
Yun et al., 2006 (62)†	37 (n = 179)	24 (n = 179)	44 (n = 179)	24 (n = 136)
Lee et al., 2005 (63)†	29 (n = 79)	22 (n = 89)	37 (n = 89)	18 (n = 56)
Lee et al., 2005 (64)†	32 (n = 25)	38 (n = 26)	50 (n = 26)	16 (n = 19)
Kim et al., 2004 (65)†	27 (n = 26)	NR	19 (n = 26)	24 (n = 21)
Range	27–37	22–38	19–50	16–24

*EEG indicates electroencephalogram; PET, positron emission tomography; SPECT, single photon emission computed tomography.
†There may be overlap in the patients studied in the studies by Yun et al., (62) Lee et al., (63) Lee et al. (64) and Kim et al. (64)

The study by Ollenberger et al. (82) assessed the role of FDG-PET in the diagnosis and management of children with refractory epilepsy through surveying epileptologists about the management of their patients' epilepsy. The purpose of the survey was to assess if the FDG-PET results changed patient management. Three epileptologists responded to the survey in reference to 108 patients. The mean age of patients was 7.3 years (SD, 3.4 years; range, 0.5–12.5 years). For surgical candidates, PET resulted in surgery being excluded (major change) in 39% of patients, and resulted in a modification of surgery (minor change) in 19% of patients. Positron emission tomography did not influence surgery in 39% of patients. Most patients had undergone both MRI and EEG (97% and 92%, respectively) prior to the PET scan, which was initially used to determine surgical management of the patients. About 39% of patients had undergone ictal SPECT, and 19% underwent interictal SPECT prior to the PET scan.

What is the Role of Functional Brain Imaging in Presurgical Functional Mapping?

As described in the alternative technologies section of this report, the current gold standard for presurgical functional mapping is the Wada test. Briefly, the Wada test is a procedure that involves inserting a catheter through the femoral artery to the carotid artery to numb each side of the brain individually to assess function. A potential role of functional brain imaging is to replace the somewhat invasive Wada test with a noninvasive test.

There were 6 studies identified that investigated functional brain imaging in presurgical functional mapping: 5 studies using fMRI and 1 using MEG. (66-70;76) The characteristics of these studies are described in Table 22.

Table 22: Characteristics of Studies Investigating the Localization of Seizure Foci With Functional Brain Imaging*

Study	Type of Study	N	Description of Patients	Seizure Origin	Blind	Reference Standard	Male, %	Mean Age, Years
Functional Magnetic Resonance Imaging								
Benke et al., 2006 (66)	PCS (consecutive enrollment)	68	Patients with intractable partial epilepsy being considered for surgery	Right TLE—28 Left TLE—40	Yes	Wada test	NR	36.4 right TLE; 38.9 left TLE
Medina et al., 2005 (67)	PCS (consecutive enrollment)	60	Patients with seizure disorder being considered for surgery	Mixed	Yes	Clinical information, MRI	55	15.8 (SD, 8.7; range 7–44)
Sabsevitz et al., 2003 (68)	PCS (consecutive enrollment)	24	Patients with left anterior temporal lobectomy	TLE	No	Wada test	33	38.6 (SD, 8.1)
Woermann et al., 2003 (69)	PCS	100	Localization-related epilepsy	Mixed	Yes	Wada test	47	32.5 typical lateralization; 29.9 atypical lateralization
Binder et al., 1996 (70)	PCS (consecutive enrollment)	22	Patients with seizure disorder being considered for surgery	Mixed	No	Wada test	36	(range, 17–64)
Magnetoencephalography								
Papanicolaou et al., 2004 (76)	PCS	100	Surgical candidates with epilepsy	MTLE—80 FLE—15 Other—5	Yes	Wada test	47	27.3 (SD, 12.1 ; range 8–56)

* FLE refers to frontal lobe epilepsy; MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; NR, not reported; PCS, prospective cohort study; SD, standard deviation; TLE, temporal lobe epilepsy.

The prospective study by Medina et al. (67) evaluated the effect of fMRI on the diagnosis and treatment planning of 60 patients with seizure disorders who were candidates for surgery. A combination of language, motor, and visual mapping were performed in each of the patients: 53 patients had language mapping, 33 had motor mapping, and 7 had visual mapping.

Four clinical experts reviewed the patients' charts without the fMRI results and completed a questionnaire regarding the diagnosis and treatment plan for the patients; then, the 4 experts completed a similar questionnaire for each of the patients with their fMRI results included with the patient charts. The fMRI results altered the counseling for the patients and their families in 35 (58%) patients, helped to avoid Wada procedure (invasive procedure) in 38 (68%) patients, altered intraoperative mapping in 31 (52%) patients, and altered surgical planning in 25 (42%) patients, including altering the extent of resection in 4 (7%) patients.

The prospective study by Benke et al. (66) compared fMRI to the Wada test in 68 patients with epilepsy who were candidates for surgery. Using the Wada test as the reference standard, they reported the following sensitivity and specificity:

➢ 89% sensitivity and 50% specificity for frontal fMRI; and
➢ 78% sensitivity and 71% specificity for temporoparietal fMRI.

The study by Sabsevitz et al. (68) compared preoperative fMRI to the Wada test results in 24 patients with left anterior temporal lobectomy. The sensitivity and specificity reported for fMRI were 100% and 73%, respectively.

The health technology assessment by Blue Cross Blue Shield from 2003 (43) investigated the role of MEG in presurgical functional mapping. Since then, 1 additional study was identified that met the inclusion criteria for this review that compared MEG to the invasive Wada procedure.

The study by Papanicolaou et al. (76) used MEG to identify the sensorimotor cortex in 100 patients with epilepsy being considered for surgery. The Wada procedure provides information on which hemisphere has primary control of language, but it does not identify the specific location within a hemisphere. When Papnaicolaou et al. compared MEG to the Wada procedure, they found that there was agreement between them in 79 (93%) of 85 cases. They did not explain why they did not have results for the remaining 15 patients in the study. Using the Wada procedure as the gold standard, the sensitivity and specificity of MEG was 98% and 83%, respectively.

The results for presurgical functional mapping were weak in the Blue Cross Blue Shield health technology assessment. (43) There were 11 studies identified investigating MEG in presurgical functional mapping. Nine of these compared MEG to invasive functional mapping. Of these, 2 included more than 20 patients. Magnetoencephalography was compared with other invasive functional mapping measures (various technologies and tasks), making a comparison among the studies impossible. However, in 7 of the 9 studies, there was 100% agreement between MEG and invasive functional mapping. There was more agreement between MEG and invasive functional mapping than there was between MEG and ICEEG.

The results of the studies identified were added to the results of the Blue Cross Blue Shield health technology assessment in Table 23. These results are consistent with the results of the previous studies comparing MEG with invasive functional mapping.

Table 23: Studies of Presurgical Functional Mapping*

Study	Type of Study	Imaging Modality	N	Blinded	Outcome: Agreement Between MEG or fMRI and Invasive Functional Mapping Results, %
Benke et al., 2006 (66)†	Prospective	fMRI	68	Yes	75 right temporal lobe epilepsy 63 left temporal lobe epilepsy
Papanicolaou et al., 2004 (76)†	Prospective	MEG	100	Yes	93 (79/85) – no results reported for 15 patients
Sabsevitz et al., 2003 (68)†	Prospective	fMRI	24	No	81 (19/24)
Woermann et al., 2003 (69)†	Prospective	fMRI	100	Yes	Discordant : 9
Breier et al., 2001 (107)	Prospective	MEG	19	Yes	89 (17/19)
Makela et al., 2001 (108)	Prospective	MEG	12	No	100 (12/12)
Roberts et al., 2000 (109)	Retrospective	MEG	17	No	76 (13/17) good agreement 12 (2/17) moderate agreement
Breier et al., 1999 (110)	Prospective	MEG	26	Yes	100% (26/26)
Ganslandt et al., 1999 (111)	Prospective	MEG	50	No	100 (50/50)
Minassian et al., 1999 (112)	Prospective	MEG	11	No	100 (11/11)
Simos et al., 1999 (113)	Prospective	MEG	13	No	100 (13/13)
Binder et al., 1996 (70)†	Prospective	fMRI	22	No	Highly correlated (r=0.96, *P* < .0001)
Ganslandt et al., 1996 (114)	Prospective	MEG	12	No	100 (10/10)
Roberts et al., 1995 (115)	Prospective	MEG	10	Yes	100 (10/10)

*fMRI indicates functional magnetic resonance imaging; MEG, magnetoencephalography.
†Studies published since the Blue Cross Blue Shield health technology assessment.

Thus, presurgical functional mapping with MEG seems to agree consistently with invasive functional mapping measurements. Functional MRI appears to have high agreement with invasive functional mapping as well. There were no studies identified that compared fMRI to MEG for presurgical functional mapping.

Results: Multiple Sclerosis

What is the Role of Functional Brain Imaging in the Diagnosis of Multiple Sclerosis?

There has been a tremendous quantity of literature published on imaging of MS in order to further understand the pathogenesis of the disease; however, there were no studies identified that were eligible for inclusion on the clinical utility of functional brain imaging in the diagnosis of MS.

Results: Parkinson's Disease

This review addressed 2 questions regarding the role of functional brain imaging for patients with PD. The first involves using functional brain imaging in the initial diagnosis of PD; the second question investigates the role of functional brain imaging in the diagnosis of parkinsonian syndromes.

What is the Role of Functional Brain Imaging in the Diagnosis of Parkinson's Disease?

The study by Eckert et al. (79) investigated the role of FDG-PET in the diagnosis of PD and in the diagnosis of parkinsonian syndromes. They included 43 patients with early PD and compared them using FDG-PET with 22 normal controls. Compared with clinical diagnosis, the sensitivity and specificity to diagnose PD was 100% and 91%, respectively (Table 24). This study did not report how the use of PET in the diagnosis of PD changes patient treatment or clinical outcomes.

Table 24: Characteristics of Functional Brain Imaging Studies for the Diagnosis of Parkinson's Disease*

Study	Type of Study	Imaging Modality	N	Readers/ Blinding	Refer-ence Standard	Male, %	Mean (SD) Age, Years	Follow-Up, Years	Sensitivity, %	Specificity, %
Eckert et al., 2005 (79)	Cohort-control	FDG-PET	43 early PD 22 control	1 reader blinded to clinical diagnosis	Clinical diagnosis	51	60.6 (10.4)	Mean, 2.1	100	91

*FDG indicates 18F-labelled-fluorodeoxyglucose; PD, Parkinson's disease; PET, positron emission tomography; SD, standard deviation.

What is the Role of Functional Brain Imaging in the Diagnosis of Parkinsonian Syndromes?

Studies investigating the diagnosis of parkinsonism used PET imaging with glucose metabolism or receptor binding. (116) For glucose metabolism FDG PET is used. Patients with PD show increased metabolism in the lentiform nucleus, thalamus, pons, and cerebellum, and there is decreased metabolism in the lateral frontal, paracentral and parietal areas. (116) Patients with MSA show decreased metabolism in the lentiform nucleus and cerebellum. (116) In patients with progressive supranuclear palsy, glucose metabolism is decreased in the frontal cortex. (116)

FDOPA PET allows for assessment of the functionality of the presynaptic nigrostriatal dopaminergic projections. FDOPA is a surrogate measure of endogenous dopamine synthesis. FDOPA uptake is reduced in parkinsonian patients and can differentiate PD from healthy subjects (even in early disease states). (116)

There were 3 studies identified that used PET in the assessment of parkinsonian syndromes that met the inclusion criteria for this review. (79-81) Table 25 describes the characteristics of these 3 studies.

Table 25: Characteristics of Functional Brain Imaging Studies in the Diagnosis of Parkinsonian Syndromes*

Study	Type of Study	Imaging Modality	N	Blind	Reference Standard	Male, %	Mean (SD) Age, Years	Drop-Outs/ Losses	Follow-Up, Years
Eshuis et al., 2006 (80)	Pros-pective cohort	F-DOPA-PET FP-CIT SPECT	13 de novo PD 17 advanced PD	No	H&Y stage, UPDRS-III	83	De novo: 54 (11) Advanced: 64 (6)	None reported	NR
Eckert et al., 2005 (79)	Pros-pective cohort	FDG-PET	135 with parkinsonism	Yes	Clinical diagnosis	51	60.6 (10.4)	53: lack of follow-up data; 17 structural abnormalities on MRI	Mean, 2.1

Study	Type of Study	Imaging Modality	N	Blind	Reference Standard	Male, %	Mean (SD) Age, Years	Drop-Outs/ Losses	Follow -Up, Years
Schreckenber ger et al.., 2004 (81)	Cohort-control	18F-DMFP PET (patients off dopamine 48 hrs prior to PET)	35 with parkinsonism 16 male healthy volunteers	Yes	Clinical diagnosis	49	64.9 (9.1; (range, 43–77; median, 65)	None reported	NR

*DMFP indicates, dorsal medial prefrontal cortex; FDG,18F-laabelled-fluorodeoxyglucose; FDOPA, fluorodopa ; FP CIT, fluoropropyl ß-carbomethoxy-3 ß-4-iodophenyltropane; H&Y refers to Hoehn & Yahr stage; MRI, magnetic resonance imaging; NR, not reported; PD, Parkinson's disease; PET, positron emission tomography, SD, standard deviation; SPECT, single photon emission computed tomography; UPDRS-III, Unified Parkinson's Disease Rating Scale, motor function.

Values referring to the accuracy of PET in the 3 studies are listed in Table 26. The sensitivity and specificity for PET is quite high for all 3 studies, even though all 3 studies used different radiotracers. The study by Eckert et al. (79) reported the use of FDG-PET in the diagnosis of patients with PD and in the diagnosis of parkinsonian syndromes. It is not clear if the addition of PET in the clinical diagnosis of PD or parkinsonian syndromes changed the treatment outcomes in patients with these conditions.

Table 26: Accuracy of Functional Brain Imaging in the Evaluation and Diagnosis of Parkinsonian Syndromes*

Study	Imaging Modality	N	Reference Standard	Sensitivity, %	Specificity, %
Eshuis et al., 2006 (80)	F-DOPA PET	30	H&Y stage, UPDRS-III	88	77
	FP-CIT SPECT			88	70
Eckert et al., 2005 (79)	FDG-PET	135	Clinical diagnosis	92	95
Schreckenberge r et al.., 2004 (81)	18F-DMFP PET	35	Clinical diagnosis	74	100

* FDG indicates 18F-laabelled-fluorodeoxyglucose; FDOPA, fluorodopa; FP CIT, Fluoropropyl ß-carbomethoxy-3 ß-4-iodophenyltropane H&Y refers to Hoehn & Yahr stage; PET, positron emission tomography, SPECT, single photon emission computed tomography; UPDRS-III, Unified Parkinson's Disease Rating Scale, motor function.

There were no studies investigating the role of MRS that met the inclusion criteria because they did not compare MRS to a reference standard nor did they compare clinical outcomes in patients diagnosed with different modalities. For instance, in the prospective study by Watanabe et al., (117) they measured NAA/Cr) ratios with MRS to diagnose MSA. They found that patients with MSA had significantly lower NAA/Cr ratios than the normal controls or patients with PD ($P \leq .001$). They reported that using MRS they were able to differentiate MSA from PD sooner than with MRI, however, they did not report treatment outcomes in patients who have MSA distinguished from PD sooner compared with those with a delayed diagnosis.

Summary of Findings of Literature Review

Alzheimer's Disease

There is evidence to indicate that PET can accurately diagnose AD. However, at this time there is no evidence to suggest that a diagnosis of AD with PET alters the clinical outcomes of patients.

Brain Tumour

The addition of MRS or FET PET to the current standard of Gd-enhanced MRI for distinguishing malignant from benign tumours in the primary diagnosis of brain tumours provides a higher specificity than Gd-enhanced MRI alone. The clinical utility of more imaging in patients with primary tumours to distinguish malignant from benign tumours is unclear, because patients with a suspected brain tumour will likely undergo a biopsy despite additional imaging results.

The addition of MRS, FET-PET, or MRI T2 to the current standard of Gd-enhanced MRI for the differentiation of recurrence from radiation necrosis provides a higher specificity than Gd-enhanced MRI alone. The clinical utility of more imaging in patients with a suspected recurrence may have clinical utility in the monitoring of patients. Based on the evidence available, it is unclear if 1 of the imaging modalities (MRS, FET-PET, or MRI T2) offers significantly improved specificity over another.

There may be a role for fMRI in the identification of surgical candidates for tumour resection; however, this requires further research.

Epilepsy

Based on the studies available, it is unclear whether MEG has similar accuracy to ICEEG in localizing seizure foci. In the 3 studies reporting sensitivity and specificity for MEG, the range was 75% to 80% for sensitivity and 44% to 70% for specificity. In the 2 studies that compared ICEEG and MEG, the sensitivity and specificity for ICEEG ranged from 72% to 86%, and 38% to 71%, respectively. More high-quality research is needed to establish if there is a difference in accuracy between MEG and ICEEG.

The results of the studies comparing PET to noninvasive EEG did not demonstrate that PET was more accurate than noninvasive EEG at localizing seizure foci.

In the study comparing MEG to invasive functional mapping, the agreement was 93%, compared with the study comparing fMRI and invasive functional mapping, in which agreement was 63% to 75%. There may be some utility of fMRI in functional mapping; however, this needs further investigation involving comparisons to other modalities. The clinical utility of MRS has yet to be established for patients with epilepsy.

Parkinson's Disease

Positron emission tomography has high sensitivity and specificity in the diagnosis of PD and the diagnosis of other parkinsonian syndromes; however, it is unclear at this time if the addition of PET in the diagnosis of these conditions contributes to the treatment and clinical outcomes of patients.

Multiple Sclerosis

There is limited clinical utility of functional brain imaging in the management of patients with MS at this time. Diagnosis of MS is established through clinical history, evoked potentials, and MRI. Magnetic

resonance imaging can identify the multifocal white lesions and other structural characteristics of MS (personal communication, clinical expert, November 6, 2006).

There is too little evidence available at this time to draw conclusions about the role of functional brain imaging in the diagnosis or differential diagnosis of MS.

Table 27 summarizes the results of the Medical Advisory Secretariat review across all diseases.

Table 27: Summary of Clinical Utility of Functional Brain Imaging Modalities for the Conditions Reviewed*

Modality	Alzheimer's Disease	Brain Tumour	Epilepsy	Multiple Sclerosis	Parkinson's Disease
fMRI	No clinical utility at this time	Unclear—more research may define a role in the identification of candidates for tumour resection.	Unclear—needs to be compared with MEG for ability to identify sensorimotor cortex.	No clinical utility at this time.	No clinical utility at this time.
HTAs	—	—	✗ NHS, 2006	—	—
MEG	No clinical utility at this time	No clinical utility at this time—but more research could define a role in the identification of candidates for tumour resection.	Maybe—potential use as a noninvasive pre-surgical evaluation in some patients with refractory epilepsy for functional mapping and localization of seizure foci.	No clinical utility at this time.	No clinical utility at this time.
HTAs	—	—	✗ Blue Cross, 2003	—	—
MRS	No clinical utility at this time.	Maybe—if the increase in sensitivity and specificity with MRS can demonstrate an improvement in clinical outcomes	No clinical utility at this time.	No clinical utility at this time.	No clinical utility at this time.
HTAs	—	✗ Hollingworth, 2006 ✗ AHRQ, 2003 ✗ Blue Cross, 2003	✗ NHS, 2006	—	✗ Clarke, 2001
PET	No clinical utility at this time—but potential for future use as treatments improve.	Maybe—if the increase in sensitivity and specificity with PET can demonstrate an improvement in clinical outcomes.	Maybe—for patients with refractory epilepsy and inconsistent MRI and EEG results. Future research needs to address the impact of PET on patient outcomes.	No clinical utility at this time.	No clinical utility at this time—but potential for future use new radiotracers are identified.
HTAs	✗ AHRQ, 2004 ✗ Patwardhan, 2004 ✗ Gill, 2003 ✗ ECRI, 2002 ✗ AETMIS, 2001 VATAP, 1998	✗ AHRQ, 2004 ✓ AETMIS, 2001, (residual tumour) ✗ ECRI, 2002 ✗ MSAC, 2000	✗ NHS, 2006 ✓ MSAC, 2004 ✓ AETMIS, 2001 ? MSAC, 2000	—	✗ Tolosa, 2006 ✗ AHRQ, 2003

*AETMIS indicates Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé; AHRQ, Agency for Health Research and Quality; ECRI, ECRI Institute; fMRI, functional magnetic resonance imaging; HTA, health technology assessment; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; MSAC, Medical Services Advisory Committee; NHS, National Health Service ;PET, positron emission tomography; VATAP, Veteran Affairs Technology Assessment Program.

Grading of Recommendations Assessment, Development, and Evaluation Evidence Profile

Table 28 lists the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile by condition and question. (118) All of the studies identified for this review were observational, which reduced all studies to a "moderate" GRADE level at the start. The studies were generally of poor quality with a variety of limitations, including small sample sizes, heterogeneous study populations, and low quality of reporting of outcomes. Several of the studies were measuring the accuracy of the functional brain imaging technologies rather than measuring the clinical utility of the technology. Overall, the quality of the evidence of most of the studies was graded as very low or low. Exceptions were the studies comparing PET to noninvasive EEG, which consistently demonstrated that PET was not superior to noninvasive EEG in terms of 1-year postoperative outcomes.

Table 28: Grading of Recommendations Assessment, Development and Evaluation Evidence Profile*

Condition	What is the Role of Functional Brain Imaging in:	No. Observational Studies	Consistency	Directness	GRADE
Alzheimer's disease	The diagnosis of Alzheimer's disease?	4	Consistency across studies	Measured accuracy, not clinical utility	Low
Brain tumour	The detection and grading of primary tumours?	6	Used various technologies, various radiotracers with PET	Measured accuracy, not clinical utility	Very low
	The differentiation of recurrence from radiation necrosis?	6	Used various technologies, various radiotracers with PET	Measured accuracy, not clinical utility	Very low
	The selection of surgical candidates for tumour resection?	2	Inconsistent results on clinical utility of fMRI	Okay	Low
Epilepsy	The localization of seizure foci in people with refractory epilepsy being considered for surgery--MEG vs. ICEEG	5	Inconsistent	Measured area resected, risk of confounders	Very low
	The localization of seizure foci in people with refractory epilepsy being considered for surgery--MEG vs. noninvasive EEG	4	Consistent	Reported various outcomes	Low
	The localization of seizure foci in people with refractory epilepsy being considered for surgery--PET vs. noninvasive EEG	4	Consistent	Measured localization and seizure outcome	Moderate
	The presurgical functional mapping of people with refractory epilepsy being considered for surgery?	5	Consistent	Measured accuracy, not clinical utility	Low
Multiple sclerosis	The diagnosis of multiple sclerosis?	0	N/A	N/A	N/A

Condition	What is the Role of Functional Brain Imaging in:	No. Observational Studies	Consistency	Directness	GRADE
Parkinson's disease	The diagnosis of Parkinson's disease?	1	Only 1 study	Measured accuracy, not clinical utility	Very low
	The differential diagnosis of parkinsonian syndromes?	3	Studied various radiotracers	Measured accuracy, not clinical utility	Very low

*EEG indicates electroencephalogram; fMRI, functional magnetic resonance imaging; ICEEG, intracranial electroencephalogram; MEG, magnetoencephalography, N/A, not applicable; PET, positron emission tomography.

Economic Analysis

The Medical Advisory Secretariat did not do a cost-effectiveness analysis, because the effectiveness of functional brain imaging has not been established for the conditions investigated in this review.

Existing Guidelines for Use of Technology

Aetna, 2006: Magnetic Source Imaging/Magnetoencephalography

Aetna (119) reviewed MEG in 2006 and concluded that the technology was "experimental and investigational" because there is inadequate evidence in the medical literature indicating that it is effective in influencing the management and improving outcomes of patients.

Centers for Medicare and Medicaid Services, 2005

The Centers for Medicare and Medicaid Services (120) published a list of all conditions under which FDG-PET scans are covered. In this list are several indications for cancer staging and diagnosis; however, tumours of the CNS are not on the list. Positron emission tomography scans for brain tumours may be covered if the PET scan is performed as part of a clinical trial that meets the requirements of the Food and Drug Administration's (FDA) category B investigational device exemption, or is a clinical trial designed to assist in patient management.

The Centers for Medicare and Medicaid Services provides coverage for FDG-PET in patients with refractory epilepsy undergoing presurgical evaluation. This publication from 2005 does not comment on the use of PET scanning in patients with AD, PD, or MS.

Policy Development

Because the clinical utility of functional brain imaging in patients with AD, PD, or MS has not been established at this time, most of the policy development section will focus on functional brain imaging for brain tumours and epilepsy, where there is potential clinical utility for functional brain imaging.

Diffusion

The rate of diffusion of fMRI and MRS is unclear because both these technologies are performed using the MRI platform and there are no specific diagnostic or Ontario Health Insurance Plan billing codes for fMRI or MRS. Most, if not all, MRI systems have fMRI and MRS capability with the appropriate software.

Magnetoencephalography

There are likely fewer than 75 MEG systems worldwide. In Ontario, there are 2 MEG systems: 1 for clinical and research use at the Hospital for Sick Children and another for research use only at Baycrest's Rotman Research Institute. Toronto Western Hospital anticipates that it will acquire a MEG within the next year. Elsewhere in Canada, there is a MEG system in Vancouver and another in Montreal, with the latter to get another in 2007. In 2005, the Hospital for Sick Children performed 94 MEG tests in patients with epilepsy (personal communication, clinical expert, December 1, 2006).

Positron Emission Tomography

In 2006, Hastings and Adams (121) reported results of a joint project of INAHTA on the diffusion of PET. They surveyed members of INAHTA on the diffusion, assessment, and clinical use of PET. There was a 69% response rate among the health technology assessment agencies surveyed (27 INAHTA agencies from 19 countries responded). Two from Canada completed the survey: the Alberta Heritage Foundation for Medical Research and Canadian Agency for Drugs and Technologies in Health.

The results of the survey indicated that there are a mean of 16.4 PET scanners per country (median, 9.5 scanners; range, 2–80 scanners). Belgium has the most per million population (1.26), followed by Denmark (1.2), and Austria (1.1). Spain (0.33 per million population), the United Kingdom (0.28), and the Netherlands (0.25) had the fewest number of PET scanners per million population. According to the results of the survey, Canada has 0.39 PET scanners per million population. The study also reported that Ontario planned to install 3 additional PET or PET/CT hybrid scanners in the near future.

In a review of PET scanning by AETMIS (29) in 2001, the number of PET scanners internationally was identified. The review authors reported the number of dedicated PET scanners (other PET scanners have CT functionality—hybrid scanners) by country between 1999 and 2001.

Table 29 lists the findings of these 2 reports and compares, where possible, the change in the number of PET scanners per country.

There were no decreases in the number of PET scanners per country over the period investigated; the only country where there was no increase in the number of PET scanners was Finland. France and Germany had the most notable increase in the number of PET scanners (up by 46 in France and 45 in Germany).

Table 29: International Diffusion of Positron Emission Tomography Scanners Between 1999 and 2004*

Country	1999–2001 (29)		2003–2004 (121)		Change in Dedicated Scanners	Change in Scanners per Million Population
	Number of Dedicated PET Scanners (Total No.)	Scanners per 1 Million Population	Number of Dedicated PET Scanners (Total No.)	Scanners per Million Population		
Canada	8 (8)	0.20	10 (10)	0.39	+2	+0.1
United States	75 (120)	0.40		NR		N/A
Japan	37 (37)	0.30		NR		N/A
China	12 (12)	0.01		NR		N/A
Germany	35 (73)	0.90	80 (80)	1.00	+45	+0.1
United Kingdom	7 (11)	0.20	16 (16)	0.28	+9	+0.08
Belgium	5 (9)	0.90	9 (13)	1.26	+4	+0.36
Russia	2 (9)	0.10		NR		N/A
Italy	8 (9)	0.20		NR		N/A
France	4 (7)	0.10	50 (50)	0.83	+46	+0.73
Austria	2 (2)	NR	9 (9)	1.13	+7	N/A
Czech Republic	1 (1)	NR		NR		N/A
Denmark	2 (2)	NR	3 (6)	1.20	+1	N/A
Finland	2 (2)	NR	2 (2)	0.38	—	N/A
Hungary	1 (1)	NR		NR		N/A
Netherlands	3 (3)	NR	4 (4)	0.25	+1	N/A
Spain	3 (3)	NR	13 (13)	0.33	+10	N/A
Sweden	2 (2)	NR	5 (5)	0.57	+3	N/A
Switzerland	3 (3)	NR		NR		N/A
Australia		NR	9 (13)	0.65		N/A
Israel		NR	1 (3)	0.46		N/A
Total	212 (314)	N/A	211 (224)	N/A		N/A

*N/A refers to not applicable; NR, not reported; PET, positron emission tomography..

Target Population

Based on the literature and administrative data from the Provincial Health Planning Database (PHPDB), the potential number prevalent epilepsy cases eligible for surgery is estimated to be 9,375 (Figure 3). However, the rate of patients choosing to undergo surgery worldwide is much lower than the number of patients who are eligible for surgery. For instance, it is estimated that 100,000 patients would be eligible for epilepsy surgery in the United States, but there are only about 2,000 epilepsy surgeries performed annually in the U.S. (2% of eligible patients). (122) Based on survey results, Engel & Shewmon (105) reported results that 1,500 surgeries for epilepsy were performed in the U.S. in 1990.

Rationale for difference between need and utilization of epilepsy surgery suggested in a review of epilepsy surgery by Siegel (122):
- Lack of awareness by primary care physicians
- Patient preference to tolerate seizures rather than undergo surgery
- Lack of third-party funding for procedure (in U.S.)

If we assume that in Ontario there is the same proportion of actual surgeries/eligible patients as the U.S. (i.e. 2%), then we would expect there to be about 188 epilepsy surgeries in Ontario per year. This is consistent with administrative data from the PHPDB which identified ~150 epilepsy surgeries per year.

Patients in Ontario are waiting 6 months-2 years for a presurgical evaluation depending on the centre.
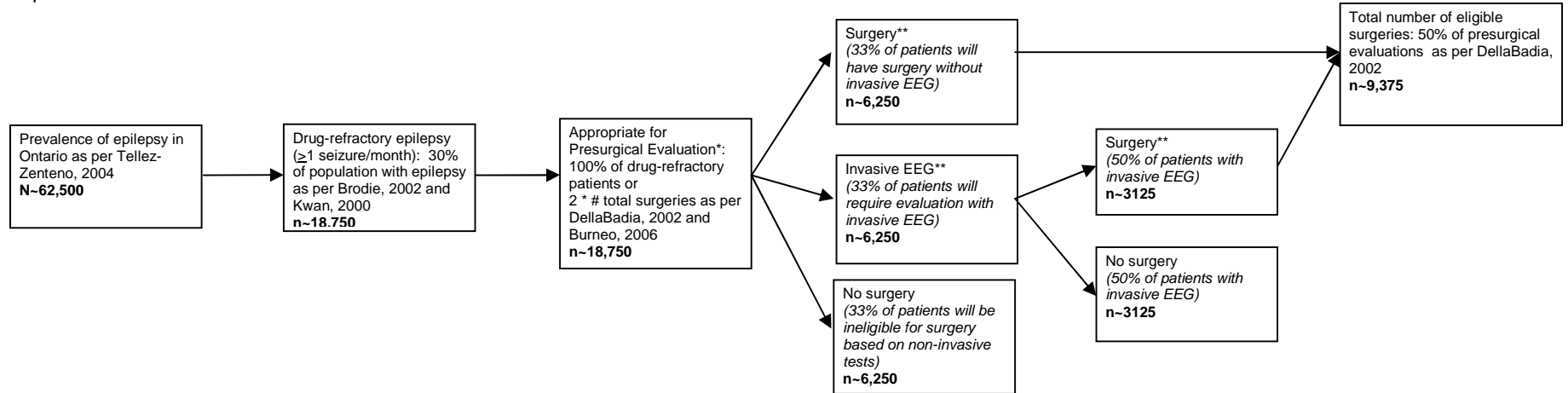
The mean hospital stay for the presurgical evaluation (including MRI, neuropsychological testing, non-invasive EEG, and potentially invasive EEG) is 16.5 days. The mean stay for the actual surgery is 7.2 days. The total mean stay is 23.7 days.

In 2005 the Institute for Clinical Evaluative Sciences published a report on Health Human Resources for Neurosurgical Services in Ontario. (123) In the report they outlined the demand for neurosurgical services, and offered recommendations on how to manage the demand. Among their recommendations, they recommended increasing the number of neurosurgeons in Ontario by 10 (from 65 to 75) and to offer alternative funding plans to neurosurgeons.

Based on administrative data, it appears that there are approximately 150 surgical resections performed in patients with epilepsy in Ontario per year. In Ontario there is up to a 2-year waiting list for adults with epilepsy to have the preliminary video EEG test to see if they are potential candidates for surgery. (Personal communication, clinical expert, December 8, 2006) It is unclear if the waiting list is as long for children. However, after preliminary testing with video EEG, children will wait an additional 6 to 8 months for ICEEG. Children who do not require ICEEG, have their surgeries performed sooner (usually within 2-3 months of video EEG monitoring). The reason for the long delay for ICEEG testing is due to the financial and human resources costs of the test. Patients are monitored in hospital for a week after the invasive procedure to place the electrodes, and then the electrodes need to be removed again.

Figure 3. Prevalent Epilepsy Population in Ontario

Population of Ontario:

Prevalence of epilepsy in Ontario as per Tellez-Zenteno, 2004
N~62,500

→

Drug-refractory epilepsy (≥1 seizure/month): 30% of population with epilepsy as per Brodie, 2002 and Kwan, 2000
n~18.750

→

Appropriate for Presurgical Evaluation*: 100% of drug-refractory patients or 2 * # total surgeries as per DellaBadia, 2002 and Burneo, 2006
n~18,750

Surgery**
(33% of patients will have surgery without invasive EEG)
n~6,250

Invasive EEG**
(33% of patients will require evaluation with invasive EEG)
n~6,250

No surgery
(33% of patients will be ineligible for surgery based on non-invasive tests)
n~6,250

Surgery**
(50% of patients with invasive EEG)
n~3125

No surgery
(50% of patients with invasive EEG)
n~3125

Total number of eligible surgeries: 50% of presurgical evaluations as per DellaBadia, 2002
n~9,375

0-14 years: 2,262,900
>15 years: 10,424,100 (124)
Prevalence of epilepsy in Ontario:
5.2/1000 (Canadian Community Health Survey data) (10)
3.6-3.7/1000 for childhood epilepsy (125)
* Presurgical evaluation includes non-invasive EEG, MRI, neuropsychological testing, and potentially other non-invasive tests
** Derived from administrative data, Provincial Health Planning Database

Patient Outcomes

Patient outcomes varied slightly according to the imaging modality and the condition that they were being investigated for. For patients with suspected AD, patient outcomes included accurate diagnosis of AD with PET.

For patients with suspected brain tumour, the patient outcome for fMRI was disability after surgery (motor, language, sensory). The patient outcomes for MEG were extent of resection, survival, tumour recurrence, and disability after surgery (motor, language, sensory). For MRS and PET, the patient outcomes were extent of resection, survival, and tumour recurrence.

The patient outcomes for patients with epilepsy undergoing MEG were freedom from seizures and disability after surgery (motor, language, sensory). For fMRI the outcome was disability after surgery, and for PET the outcome was freedom from seizures.

The patient outcomes for PD were accurate diagnosis of PD or parkinsonian syndromes with PET or MRS.

Ethical and/or Legal Considerations

It is unknown whether MEG can replace ICEEG in some patients with refractory epilepsy undergoing presurgical evaluation. However, to conduct an RCT comparing MEG with ICEEG in patients with epilepsy may be viewed as unethical because ICEEG could be considered medically necessary. A possible solution to this would be to randomized patients to MEG with ICEEG, and ICEEG alone. However, this design is subject to bias because it would be difficult to be sure that the MEG results alone influenced surgery, rather than the combination of the 2 technologies.

Financial Impact

If MEG can replace ICEEG in some patients, then there would be an expected cost savings because patients will not require the 2 surgeries involved with ICEEG (1 to insert electrodes, another to remove the electrodes—often done at time of surgery for resection if indicated), nor will the patients require the additional hospital time to monitor the ICEEG.

Human Resources Impact

For MEG, a specially-trained MEG technician performs the studies and collects the data. In addition, an EEG technician performs the EEG studies in conjunction with the MEG. A specialized MEG physician (neuroradiologist, neurophysiologist) interprets the results of the MEG, which is very time-consuming. Patients will also undergo a MRI, requiring MRI human resources as well.

The following is a list of human resource requirements for producing radioisotopes used in PET scanning: (29)

- cyclotron laboratory personnel, including a cyclotron operator, radiochemist, and radiopharmacist;
- a nuclear medicine specialist who determines the amount of radioisotope to be shipped;
- a radiation protection supervisor who oversees production and shipment of radiotracer;
- a carrier licensed by Health Canada to transport radioisotopes; and
- a nuclear medicine specialist to receive shipments of radioisotopes.

System Pressures

The MEG procedure lasts 3 to 5 hours, depending on the patient and the number of tests required. Currently, the Hospital for Sick Children uses the MEG system 3 days a week for clinical cases. It performs the MEG procedure on an estimated 3 patients per week (about 150 patients per year). Most of the patients are children; however, the system is used occasionally for adults who have been referred from other institutions. The Toronto Western Hospital refers an estimated 3 patients per month to the Hospital for Sick Children for MEG evaluation (personal communication, clinical expert, November 23, 2006).

Because the MEG procedure can last for several hours (patients take breaks throughout the procedure), and given that most of the patients studied at the Hospital for Sick Children are children, patients are usually sleep-deprived upon arrival, so that they can sleep through the MEG procedure without having to undergo sedation (which may interfere with the results of the MEG). Electroencephalogram is performed at the same time at the MEG. One technologist is required for the MEG system and another for the EEG.

Patients undergo MEG and MRI in the same day (usually after the MEG procedure). It takes several hours and substantial expertise to analyze and integrate the data captured with the MEG, MRI, and EEG. If the results of the tests indicate that the patient is eligible for surgery, then the images and data collected are used to guide the neurosurgery.

It takes 1 to 2 years from the initiation of the presurgical evaluation to surgery. Patients typically wait 6 to 8 months for the initial presurgical evaluation with noninvasive EEG with video monitoring. If necessary, the ICEEG is scheduled on average 6 months later, and then surgery is performed 6 to 8 months after ICEEG. If the patient does not require ICEEG, then the surgery may be completed sooner. Because the ICEEG can take 5 to 10 days, hospitals have dedicated beds for EEG; thus, they can only perform a specified number of tests per month.

Stakeholder Analysis

If MEG could replace ICEEG in some cases, then there would be an increased demand for MEG, requiring more technicians and MEG systems. The MEG results are very time-consuming to analyze, and analysis of the data requires training and practice.

Glossary

Alzheimer's Disease A progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain leading to loss of cognitive function such as attention, memory, and language

Brain tumour Any intracranial tumor created by abnormal and uncontrolled cell division, normally either in the brain itself (neurons, glial cells, astrocytes, oligodendrocytes, ependymal cells), lymphatic tissue, (blood vessels), in the cranial nerves (myelin-producing Schwann cells), in the brain envelopes (meninges), skull, pituitary and pineal gland, or spread from cancers primarily located in other organs (metastatic tumors)

Computed tomography Radiography in which a three-dimensional image of a body structure is constructed by computer from a series of plane cross-sectional images made along an axis

Electroencephalography A diagnostic test of electrical activity in the brain

Elequent cortex The regions of the brain responsible for motor, sensory, and language function

fMRI An type of MRI that detects the changes in red blood cells and capillaries as they deliver oxygen to "functioning" parts of the brain

Frontal lobe epilepsy A type of epilepsy that originates in the frontal lobe of the brain, usually involving a cluster of short seizures with a sudden onset and termination

Focus The location in the brain from which epileptic charges originate

Ictal Events during a seizure

Interictal Period between seizures (typically > 24 hours)

Lateral temporal lobe epilepsy Arises in the neocortex on the outer surface of the temporal lobe of the brain

Magnetic resonance spectroscopy Used to measure the levels of different metabolites in body tissues. The MR signal produces spectrum of difference resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain, as well as to provide information on tumor metabolism

Magnetoencephalography	An imaging technique used to measure the magnetic fields produced by electrical activity in the brain via extremely sensitive devices such as superconducting quantum interference devices, for locating pathology and determining function
Mesial temporal lobe epilepsy	Arises in the hippocampus, parahippocampal gyrus and amygdala which are located in the inner aspect of the temporal lobe
Multiple sclerosis	A progressive, inflammatory, demyelinating disease of the central nervous system
Occipital lobe epilepsy	Seizures that originate in the occipital lobe of the brain, usually beginning with visual hallucinations, rapid eye blinking or other eye-related symptoms
Parkinson's Disease	A progressive nervous disease occurring most often after the age of 50, associated with the destruction of brain cells that produce dopamine and characterized by muscular tremor, slowing of movement, partial facial paralysis, peculiarity of gait and posture, and weakness
PET	A computerized imaging technique that allows imaging of cerebral metabolic rates, receptor densities, and blood flow. Most commonly, radioactive labeled F-fluoro-2-deoxyglucose assesses cerebral glucose metabolism
Postictal	Time immediately following a seizure
SPECT	A scanner that measures a low-dose radioactive material as it circulates through the brain. SPECT can track cerebral blood flow and detect alternations in brain metabolism between and during seizures
Temporal lobe epilepsy	Rrecurrent epileptic seizures arising from one or both temporal lobes of the brain. Two main types are mesial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE)

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Appendices

Appendix 1: Literature Search Strategies

Alzheimer's Disease

Search date: September 2, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 4 2006>
Search Strategy:
----
1   exp Magnetic Resonance Spectroscopy/ (58093)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (41955)
3   positron emission tomography.mp. or exp Positron-Emission Tomography/ (12914)
4   exp Magnetoencephalography/ or magnetoencephalography.mp. [mp=title, original title, name of substance word, subject heading word] (2576)
5   *tomography, emission-computed/ (6646)
6   fmri.mp. (6022)
7   (functional and (MRI or MR or magnetic resonance imaging)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (13937)
8   (functional imaging or neuroimaging).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9686)
9   or/1-8 (97099)
10   exp Alzheimer Disease/ (24647)
11   9 and 10 (1056)
12   limit 11 to (humans and english language and yr="2000 - 2006") (667)
13   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (296345)
14   12 and 13 (30)
15   12 (667)
16   limit 15 to (case reports or comment or editorial or letter or "review") (202)
17   15 not 16 (465)
18   limit 17 to "diagnosis (sensitivity)" (236)
19   14 or 18 (256)

Database: EMBASE <1980 to 2006 Week 35>
Search Strategy:
----
1   exp Nuclear Magnetic Resonance Spectroscopy/ (23673)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (32710)
3   positron emission tomography.mp. or exp Positron Emission Tomography/ (30339)
4   fmri.mp. or exp Functional Magnetic Resonance Imaging/ (7689)
5   magnetoencephalography.mp. or exp MAGNETOENCEPHALOGRAPHY/ (2876)
6   functional imaging.mp. (2695)
7   exp neuroimaging/ (8192)
8   or/1-7 (79002)
9   exp ALZHEIMER DISEASE/ (49328)
10   8 and 9 (1961)
11   limit 10 to (human and english language and yr="2000 - 2006") (1033)
12   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (373557)
13   11 and 12 (58)
14   11 (1033)
15   limit 14 to (editorial or letter or note or "review") (392)
16   Case Report/ (901734)
17   14 not (15 or 16) (605)
18   limit 17 to "diagnosis (sensitivity)" (347)
19   13 or 18 (393)

Brain Tumours

Search date: September 1, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 4 2006>
Search Strategy:
----
1   exp Magnetic Resonance Spectroscopy/ (58093)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (41955)
3   positron emission tomography.mp. or exp Positron-Emission Tomography/ (12914)
4   exp Magnetoencephalography/ or magnetoencephalography.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2576)
5   *tomography, emission-computed/ (6646)
6   fmri.mp. (6022)
7   (functional and (MRI or MR or magnetic resonance imaging)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (13937)
8   (functional imaging or neuroimaging).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9686)
9   or/1-8 (97099)
10   exp Brain Neoplasms/ (29296)

11   9 and 10 (2067)
12   limit 11 to (humans and english language and yr="2000 - 2006") (1215)
13   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (296345)
14   12 and 13 (16)
15   12 (1215)
16   limit 15 to (case reports or comment or editorial or letter or "review") (535)
17   15 not 16 (680)
18   limit 17 to "diagnosis (sensitivity)" (442)
    19   14 or 18 (451)

Database: EMBASE <1980 to 2006 Week 35>
Search Strategy:

----
1   exp Brain Tumor/ (46628)
2   exp Brain Cancer/ (2494)
3   exp Nuclear Magnetic Resonance Spectroscopy/ (23673)
4   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (32710)
5   positron emission tomography.mp. or exp Positron Emission Tomography/ (30339)
6   fmri.mp. or exp Functional Magnetic Resonance Imaging/ (7689)
7   magnetoencephalography.mp. or exp MAGNETOENCEPHALOGRAPHY/ (2876)
8   functional imaging.mp. (2695)
9   exp neuroimaging/ (8192)
10   or/3-9 (79002)
11   exp Brain Tumor/ or exp Brain Cancer/ (46628)
12   10 and 11 (2032)
13   limit 12 to (human and english language and yr="2000 - 2006") (1132)
14   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (373557)
15   13 and 14 (27)
16   13 (1132)
17   limit 16 to (editorial or letter or note or "review") (379)
18   Case Report/ (901734)
19   16 not (17 or 18) (531)
20   limit 19 to "diagnosis (sensitivity)" (371)
21   15 or 20 (390)

Epilepsy

Search date: September 1, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations,
EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 4 2006>
Search Strategy:
----
1   exp Magnetic Resonance Spectroscopy/ (58093)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, original title, abstract, name of
substance word, subject heading word] (41955)
3   positron emission tomography.mp. or exp Positron-Emission Tomography/ (12914)
4   exp Magnetoencephalography/ or magnetoencephalography.mp. [mp=title, original title, abstract,
name of substance word, subject heading word] (2576)
5   *tomography, emission-computed/ (6646)
6   fmri.mp. (6022)
7   (functional and (MRI or MR or magnetic resonance imaging)).mp. [mp=title, original title, abstract,
name of substance word, subject heading word] (13937)
8   (functional imaging or neuroimaging).mp. [mp=title, original title, abstract, name of substance word,
subject heading word] (9686)
9   or/1-8 (97099)
10   exp Epilepsy/ (33384)
11   9 and 10 (2384)
12   limit 11 to (humans and english language and yr="2000 - 2006") (1418)
13   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, original title,
abstract, name of substance word, subject heading word] (296345)
14   12 and 13 (18)
15   12 (1418)
16   limit 15 to (case reports or comment or editorial or letter or "review") (634)
17   15 not 16 (784)
18   limit 17 to "diagnosis (sensitivity)" (445)
19   14 or 18 (460)

Database: EMBASE <1980 to 2006 Week 35>
Search Strategy:
----
1   exp Nuclear Magnetic Resonance Spectroscopy/ (23673)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, abstract, subject headings, heading
word, drug trade name, original title, device manufacturer, drug manufacturer name] (32710)
3   positron emission tomography.mp. or exp Positron Emission Tomography/ (30339)
4   fmri.mp. or exp Functional Magnetic Resonance Imaging/ (7689)
5   magnetoencephalography.mp. or exp MAGNETOENCEPHALOGRAPHY/ (2876)
6   functional imaging.mp. (2695)
7   exp neuroimaging/ (8192)
8   or/1-7 (79002)
9   exp Epilepsy/ (64653)
10   8 and 9 (3003)
11   limit 10 to (human and english language and yr="2000 - 2006") (1535)
12   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject
headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

(373557)
13   11 and 12 (18)
14   11 (1535)
15   limit 14 to (editorial or letter or note or "review") (426)
16   Case Report/ (901734)
17   14 not (15 or 16) (766)
18   limit 17 to "diagnosis (sensitivity)" (478)
19   13 or 18 (493)

Multiple Sclerosis

Search date: August 15, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations,
EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 1 2006>
Search Strategy:
----
1   exp Magnetic Resonance Spectroscopy/ (57712)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, original title, abstract, name of
substance word, subject heading word] (41674)
3   positron emission tomography.mp. or exp Positron-Emission Tomography/ (12759)
4   exp Magnetoencephalography/ or magnetoencephalography.mp. [mp=title, original title, abstract,
name of substance word, subject heading word] (2564)
5   *tomography, emission-computed/ (6644)
6   fmri.mp. (5943)
7   (functional and (MRI or MR or magnetic resonance imaging)).mp. [mp=title, original title, abstract,
name of substance word, subject heading word] (13807)
8   (functional imaging or neuroimaging).mp. [mp=title, original title, abstract, name of substance word,
subject heading word] (9602)
9   or/1-8 (96341)
10   exp Multiple Sclerosis/ (12061)
11   9 and 10 (533)
12   limit 11 to (humans and english language and yr="2000 - 2006") (348)
13   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, original title,
abstract, name of substance word, subject heading word] (293907)
14   12 and 13 (22)
15   12 (348)
16   limit 15 to (case reports or comment or editorial or letter or "review") (125)
17   15 not 16 (223)
18   limit 17 to "diagnosis (sensitivity)" (107)
19   14 or 18 (125)

Database: EMBASE <1980 to 2006 Week 32>
Search Strategy:
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1   exp Nuclear Magnetic Resonance Spectroscopy/ (23468)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (32745)
3   positron emission tomography.mp. or exp Positron Emission Tomography/ (30049)
4   fmri.mp. or exp Functional Magnetic Resonance Imaging/ (7535)
5   magnetoencephalography.mp. or exp MAGNETOENCEPHALOGRAPHY/ (2838)
6   functional imaging.mp. (2693)
7   exp neuroimaging/ (7926)
8   or/1-7 (78408)
9   exp Multiple Sclerosis/ (25637)
10   8 and 9 (662)
11   limit 10 to (human and english language and yr="2000 - 2006") (447)
12   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (370586)
13   11 and 12 (22)
14   11 (447)
15   limit 14 to (editorial or letter or note or "review") (156)
16   Case Report/ (898210)
17   14 not (15 or 16) (263)
18   limit 17 to "diagnosis (sensitivity)" (137)
19   13 or 18 (151)

Parkinson's Disease

Search date: August 15, 2006
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 1 2006>
Search Strategy:
----
1   exp Magnetic Resonance Spectroscopy/ (57712)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (41674)
3   positron emission tomography.mp. or exp Positron-Emission Tomography/ (12759)
4   exp Magnetoencephalography/ or magnetoencephalography.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2564)
5   *tomography, emission-computed/ (6644)
6   fmri.mp. (5943)
7   (functional and (MRI or MR or magnetic resonance imaging)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (13807)
8   (functional imaging or neuroimaging).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9602)
9   or/1-8 (96341)
10   exp Parkinsonian Disorders/ (17308)
11   9 and 10 (877)

12 limit 11 to (humans and english language and yr="2000 - 2006") (535)
13 (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (293907)
14 12 and 13 (26)
15 12 (535)
16 limit 15 to (case reports or comment or editorial or letter or "review") (204)
17 15 not 16 (331)
18 limit 17 to "diagnosis (sensitivity)" (103)
19   14 or 18 (128)

Database: EMBASE <1980 to 2006 Week 32>
Search Strategy:

1   exp Nuclear Magnetic Resonance Spectroscopy/ (23468)
2   (spectroscop$ adj2 (magnetic resonance or mr)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (32745)
3   positron emission tomography.mp. or exp Positron Emission Tomography/ (30049)
4   fmri.mp. or exp Functional Magnetic Resonance Imaging/ (7535)
5   magnetoencephalography.mp. or exp MAGNETOENCEPHALOGRAPHY/ (2838)
6   functional imaging.mp. (2693)
7   exp neuroimaging/ (7926)
8   or/1-7 (78408)
9   exp parkinson disease/ or exp parkinsonism/ (36760)
10   8 and 9 (1768)
11   limit 10 to (human and english language and yr="2000 - 2006") (908)
12   (systematic$ review$ or random$ or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (370586)
13   11 and 12 (50)
14   11 (908)
15   limit 14 to (editorial or letter or note or "review") (373)
16   Case Report/ (898210)
17   14 not (15 or 16) (470)
18   limit 17 to "diagnosis (sensitivity)" (195)
19   13 or 18 (236)

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