The Role Of Functional Imaging In The Diagnosis And Treatment Of Epilepsy

Neurological conditions such as epilepsy and Schizophrenia have been ascribed to supernatural phenomena such as 'being possessed' through an ignorance of the fundamental mechanisms that govern our consciousness. For this reason, one of the most important advances in modern Neuroscience has been the advent of Functional brain imaging, which has for the first time allowed a connection to be drawn between a conscious or subconscious mental process, and a related electrophysiological change in the brain. Functional imaging has endless possible applications, with this dissertation examining how functional imaging has aided the diagnosis and treatment of epilepsy, a common neurological disorder that affects 0.5-1% of the world's industrialized population [1].

Overview of the potential of functional imaging in epilepsy

Epilepsy is defined as a chronic condition of seizures, [2] a seizure being a paroxysmal discharge of neurones causing an event which is discernable by the subject or an observer.[2]Seizures occur for many different reasons, and different aetiologies underlie different types of epilepsy.[3] The enhanced excitability seen in the EZ (see fig.1 for explanation) may result from many different factors such as altered cellular properties or altered synaptic connections caused by a local scar, blood clot or tumour.[6] The breakdown of surrounding inhibitory inputs to an EZ has been shown to create abnormal firing patterns in neurones, known as paroxysmal depolarizing shifts. (PDS)[7]. These are uncommonly long action potentials that do not generally occur in the brain. Due to this, the EZ has a greater degree of electrical activity than surrounding cortex. During the inter-ictal period (the ictal period being the seizure itself), the EZ also exhibits abnormal electrical activity, known as interictal epileptiform discharges (IEDs)[8].

Using imaging techniques that measure cerebral electrical activity, such as EEG and MEG, these areas of abnormality can be distinguished and localized. Other functional imaging techniques can be used to infer the region of abnormal activity through the observation that increased neural activation in a region causes increased blood flow to that area[9] (fMRI[10], PET[11] and SPECT[12]), and that increased activation leads to a localized increase in glucose metabolism (the basis of MRS [13]). There is insufficient space to describe the history and application of each technology within this dissertation, so only the currently relevant imaging techniques will be described in detail.

In contrast, to a partial seizure, a generalized seizure shows abnormally increased electrical activity across both hemispheres.[14] This makes functional imaging particularly valuable in making this important clinical distinction, as this diagnosis affects the drugs chosen, as well as future suitability of the patient for surgery. During diagnosis therefore, despite clinical observation and history of the patient's behaviour during a seizure being the most important

In addition to assisting in accurate diagnosis, functional imaging techniques are also

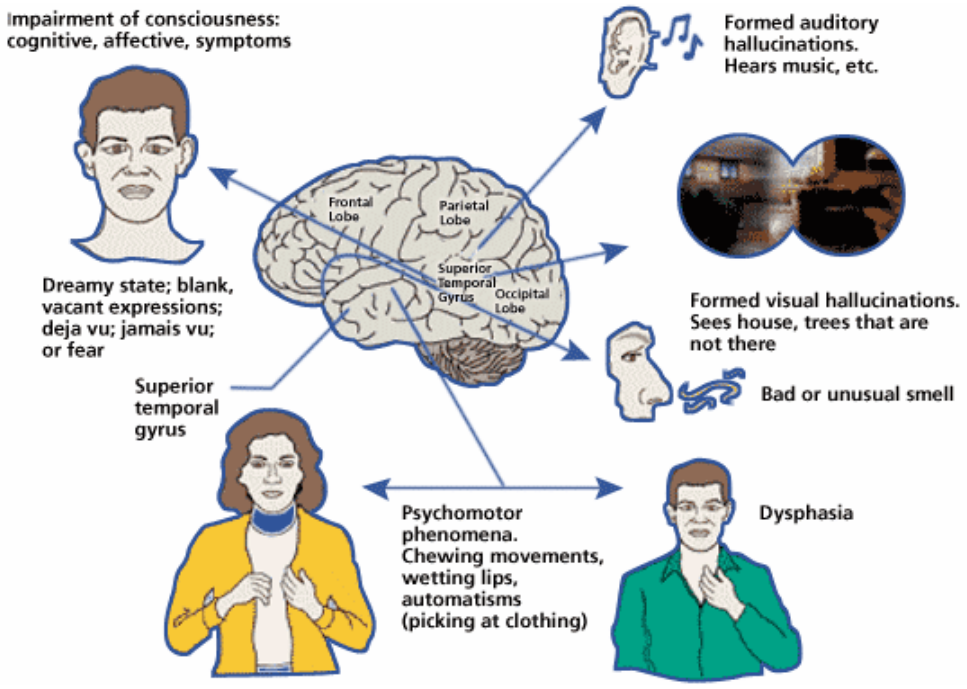

Figure 1There are two primary electrographic patterns that are used to classify seizures: the partial seizure and the generalized seizure.[4] On a scalp electroencephalogram (EEG), a form of functional imaging, abnormal electrical activity in the cortex is seen to originate from a small population of neurones (the epileptogenic zone, or EZ) from which it spreads out along existing cortical pathways.[5]The clinical manifestations of the seizure are dependent upon where the EZ originates; a partial seizure beginning in the primary motor cortex will most probably lead to the abnormal movement of the limbs, while seizures originating in the limbic system may cause changes in emotion and perception. The figure above illustrates how the symptoms of a seizure are affected by the location of the EZ. (Figure from http://www.ucbepilepsy.com/pc/images/understanding_epilepsy/seizure_types/complex.gif - UCB Pharmaceuticals epilepsy patient microsite, last accessed 26th March 2006)

extremely useful in the treatment of many different types of epilepsy. With factor[15] in diagnosis consolidation, it is clear that fu nctional imaging plays a fundamental role in this assessment. techniques such as combined EEG-fMRI, MEG and PET able to identify the exact location of the EZ in partial epilepsy, it is now possible to offer surgery that could potentially cure patients unresponsive to drug treatment of their epilepsy with a minimum of side effects –something that until recently has been exceedingly difficult and risky to do.

Functional imaging can also be used to analyze neural activity in patients attempting to decrease the dose of their anti-seizure medication, or stop completely. Methods

such as the scalp EEG can monitor any increases in abnormal brain activity as the drug plasma concentration decreases, to avoid the patient having another seizure.

The following two sections consider the application of various functional imaging techniques in both the diagnosis and treatment of epileptic seizures in greater detail, comparing and contrasting various methods.

Functional Imaging In The Diagnosis Of Epilepsy

As stated before, the prompt and accurate diagnosis of epilepsy is extremely desirable in the treatment of epilepsy, allowing evaluation of possible aetiological factors, and hence helping form a clear plan for subsequent treatment. The International Classification of Epileptic syndromes is based on two distinctions, that of localized onset partial epilepsies and generalized epilepsies, and idiopathic and symptomatic epilepsies.[16] This section examines how the different methods of functional imaging are able to contribute towards the Neurologist's accurate diagnosis.

The first aspect of diagnosis that will be examined is the classification of the type of seizure. Three main factors form the basis of this classification: anatomical assessment, clinical observation, and interictal/ictal functional imaging. Anatomical data is largely attained through MRI, superseding its predecessor the CT scan in most cases, a subject upon which further information is available in the reviews indicated.[17,18] The clinical observations that recognize the physical manifestations of the epilepsies are available in the ILAE epilepsy classification.[19] This classification uses clinical, anatomical and characteristic EEG traces to categorize epilepsies, EEG being the longest established functional neuro-imaging technique.

The electroencephalogram is the first functional imaging technique that will be discussed. In a normal subject, the resting EEG recorded from scalp electrodes demonstrates stereotyped waveforms that are reproducible amongst other control subjects. It has been known for a long time[20] that the EEG recordings in patients with epilepsy demonstrate abnormalities characteristic for different epilepsies. Figure 2 is an EEG reading taken with a patient with Tonic-clonic generalized epilepsy

However, where the diagnosis is uncertain, ictal EEG has several advantages. Firstly, the electrophysiological recording during the ictal period can confirm the diagnosis of epilepsy, as like the IEDs, EEG recordings during particular seizures tend to be characteristic of that type of seizure. Identification of these waveforms can confirm the epilepsy diagnosis over another type of episodic event that may potentially cause an abnormal EEG, such as narcolepsy.[21] Secondly, in cases where initial diagnosis is incorrect, a record of activity during the actual seizure may enable a more accurate classification. A case study of a patient who was initially mis-diagnosed using interictal EEG and clinical assessment, and as a consequence failed to respond to pharmacotherapy is a good example of the application of ictal EEG. Initially diagnosed with partial epilepsy, Ictal EEG recordings found this to be incorrect, and a re-diagnosis of primary generalized epilepsy led to a successful drug treatment that stopped the seizures. [22]

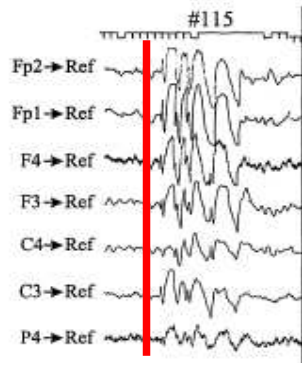

Figure 2 Shows part of an Ictal EEG recorded as the patient moved from normal into the tonic phase of a tonic-clonic generalized seizure. . Until the time point indicated with the red line, the EEG shows normal activity, as would be recorded most healthy subjects. The abnormal activity after the line is called an interictal Epileptiform Discharge (IED). IEDs vary between different epilepsies, and their differing characteristics can be correlated with clinical findings to support potential diagnosis.[1] In many cases, the interictal EEG combined with analysis of the clinical history from the patient is sufficient to accurately identify the type of epilepsy.[1]

In summary, Interictal and ictal EEG are highly established methods of recording cerebral activity, and partly due to their maturity, form the fundamental basis of the international seizure classification system. However EEG, both ictal and interictal, is not without its limitations in diagnosis. EEG records information from populations of neurones firing in the cortex, however due to the degree of signal attenuation that occurs between the recording electrode and the cortex (due to bone and fluids etc) very small IEDs may well be lost due to the poor signal to noise ratio, and spatial resolution of the electrode configuration.[23] If the epileptogenic zone is deep within the brain, the EEG will not detect it, or only detect the activity once it

has spread through cortical pathways, and hence be potentially mistaken for a generalized seizure. Artefacts from the electrocardiogram and from muscle contractions during certain seizures also affect the EEG reading, making consistent readings difficult, and considerable experience is required on the part of the neurologist in interpreting the EEG.

Another imaging technology that can be used to measure changes in electrical activity in the brain, and hence uncover abnormal patterns is magnetoecephalography (MEG). As in EEG, MEG recordings reflect the electrical activity of neuronal populations firing in the brain. The recordings are made using sensors called SQUIDS which measure the electromagnetic field generated when a current flows between the source and sink of the neurone.[24] These signals do not attenuate as they travel through tissue and bone as in EEG, improving the signal to noise ratio, but because the magnetic fields detected are so small, this gain is largely offset by the increased interference from sources of electromagnetic interference. The electrical activity generated by IED spikes can be recorded over background activity using MEG, and when this functional data is superimposed on an MRI / CT scan derived anatomical image, the source of the IED can be determined, although like EEG accuracy does decrease further away from the cortex.[25] This allows the location of the epileptogenic zone to be accurately determined, if it is a partial epilepsy, and hence a diagnosis arrived at. Furthermore, if a structural lesion or tumour is discovered near the site of the abnormal activity, then it is probable that this is the cause of the seizures, and hence previously idiopathic epilepsies may be accurately diagnosed.[26] In addition, because of the orientation of the SQUID sensors, the electrical activity detected is only in one plane, the tangential plane, as opposed to the indiscriminate mixture of radial and tangential recordings of EEG. This is significant as it simplifies 3D modelling of MEG data, making models more accurate, and hence increasing spatial resolution.[27] However the cost of the machinery (and hence its relatively sparse availability) and expertise required for interpretation currently limit this functional imaging. MEG imaging offers a great many advantages, however emerging EEG-fMRI technology, with improved spatial and temporal resolution may supersede MEG in the future in the areas of diagnosis and treatment within the field.

Positron Emission Tomography (PET)[28] scans are a powerful diagnostic tool with the ability to measure a variety of physiological parameters. A running theme in the diagnosis of epilepsy is the determination of a seizure focus, if one exists. A type of PET scan using [^{18}F]fluro-2-deoxyglucose (FDG) is able to locate variations in cerebral metabolism; a reflection of local neuronal activity.[29] An epileptogenic zone is generally less active than surrounding areas during the interictal phase, becoming more active during a seizure. This is reflected in both the blood flow to the region, and the degree of glucose metabolism; both changes can be detected by PET (blood flow using the ^{15}O marker) and the results overlaid onto an anatomical image, in a similar manner to MEG/MRI (see above). Both these methods are more suited however to the fine determination of the location of the seizure focus in preparation for surgery, as will be discussed in the next section. PET scanning does however have important drawbacks that must be appreciated when assessing its usefulness as a functional imaging technique. Although non-invasive in nature, PET scanning involves the injection of radioactive substances in order to determine the location of the tagged substance within the body.[30] This limits the number of scans possible. In addition, the short half lives of the radioactive isotopes used in PET require a cyclotron to generate the markers themselves. This makes PET a highly expensive and specialised imaging method, which is too risky and expensive to roll out on a large enough scale to make its use in diagnosis commonplace.

The final major mode of functional imaging used in epilepsy diagnosis is Magnetic Resonance Spectroscopy, or MRS.[31] MRS provides a means of investigating cerebral metabolites and some neurotransmitters. Studies using MRS (and sometimes PET) allow the changes in receptor density associated with some types of epilepsy to be studied. Such studies have led to the development of ideas regarding the breakdown in surround inhibition, being the stimulus leading to seizure onset: cortical circuits become unstable when sub-cortical homeostatic inhibition declines. However, as with other functional studies, standard MRI images must be coupled with the functional data so as to determine the specific sites of activity.[32]

Functional Imaging in the Treatment Of Epilepsy

The reason that the accuracy of diagnosis in epilepsy is so critical is to ensure that the treatment regime is best placed to have the most beneficial effect to the patient. The ultimate goal in the treatment of epilepsy is to leave the patient with no seizures and no side effects from the options available. By far the most popular and effective treatment for the majority of patients is a pharmacotheraputic regime of anti seizure medication.[33]. Anti-seizure medication is capable of completely controlling seizures in about 75% of patients. However approximately 10% of sufferers continue to have seizures at intervals of 1 month or less,[35] with the remainder experiencing seizures less often, but still having to live in fear of what might happen should one occur. The majority of this small but significant minority have partial focal epilepsy rather than a generalized condition.[34] The surgical resection of the epileptogenic zone has been shown to increase the likelihood of a previously drug-resistant patient becoming seizure free by 70%[38]. Previously however, surgery in such patients had only been considered in the most severe of cases due to the high risk involved in both the procedures essential for identifying the focus prior to resection, the surgery itself, and the risk of loss of cognitive faculties afterwards. However, as stated in the overview, developments in neural functional imaging have contributed to vastly improved outcomes from such procedures, improving the lives of thousands of people previously resigned to a lifetime of seizures.

The epileptogenic zone is defined as the area of cerebral cortex that is both necessary and sufficient to generate epileptic seizures, its entire removal being essential for a successful outcome. [35]Surrounding the epileptogenic zone, however, is so called ‘eloquent cortex’; so termed as any injury to this matter will lead to a decline in cognitive faculties. Surgery must hence avoid damage to eloquent cortex as far as is practicable.

In the past, there have been many different methods for mapping the eloquent cortex, determining the epileptogenic zone (EZ), and intrahemispheric functional mapping (determining the specific functions of surrounding eloquent cortex.) In recent years however, many of these techniques such as MRI-PET, SPECT, physical cortical stimulation mapping and video telemetry with EEG have been superseded by

the versatility of fMRI combined with EEG.[36] Krakow et al (reference 40) note the fact that although the localization of IEDs is essential to determining the EZ location, neither EEG nor MEG can localize these with sufficient accuracy, and the low temporal resolution of SPECT and PET imaging prevents the localization of brief IEDs. Therefore, the best compromise between these two extremes is fMRI coupled with EEG, the latter being able to quickly detect the generation of the IED. This IED can be functionally mapped using fMRI due to the blood oxygen level dependent effect (BOLD)[37] – essentially where an increased blood flow to the active area causes a decrease in the concentration of deoxyhaemaglobin (a paramagnetic molecule detected by the fMRI scanner). The spatial resolution of this technique alone is not especially high, but because a high resolution MRI image can be attained contemporaneously in the same plane, the site of the EZ can be very accurately determined with minimal error. This method of imaging is expected to eventually completely supersede its predecessors, although although drawbacks include the delay between the IED detection and the onset of the BOLD effect giving the IED the opportunity to spread beyond the EZ, and hence into eloquent cortex.

Functional imaging also has a place in the continual assessment of the efficacy of a patients anti-seizure medication. If a patient has been seizure free for more than a year, a doctor may wish to decrease the dose of a particular drug, due to its toxicity. Scalp EEG is used to detect IED activity, as this offers an accurate prediction as to the likelihood of future seizures. If a particular drug is being gradually withdrawn, regular EEG monitoring ensures the probability of seizures does not increase accordingly.[38] In addition, some drugs cause mental retardation, which can be irreversible[39] if not treated promptly by changing medication or withdrawing it completely. This effect can be assessed using EEG and MEG[42] with a slowing of the background waves a sign that such an event may be occurring.

Optical Imaging is an emerging field in the treatment of epilepsy, although it is very much in its infancy. Studies so far (largely in animals due to the highly invasive nature of the procedure)[40] have detected the BOLD effect in the cerebral cortex by observing changes in the reflectivity of the cortical surface using a video camera. This technique could provide fast localization of the EZ, although it is restricted to the

surface of the brain, and would currently only be possible immediately prior to surgery as the skull would need to be cut away. A non invasive study through thinned skull and infra-red cameras shows promise of a potential non invasive method, but this is still in early development.[41]

Summary

This concise overview of how functional imaging has and continues to revolutionize medical thinking on epilepsy has assessed the most important roles in the diagnosis and treatment of the condition for what are now the key technologies of today and the future, namely fMRI/EEG, MEG and potentially optical imaging. The essential aim of imaging in epilepsy has remained the same ever since the first scalp EEGs were recorded: accurately determine the type of epilepsy, its location, and use this information to achieve the ideal situation of "no seizures, no symptoms."

The advances in the technology have improved the viability of surgery as a clinical option to alleviate symptoms, with much reduced risk thanks to greater accuracy at identifying the EZ in partial epilepsy. The advances in the techniques for monitoring electrical activity in the brain have also improved and continue to do so with newer mathematical models being attempted on technologies such as MEG. These have allowed a greater sensitivity to IEDs from deeper areas of the brain, and have aided not only better disease prognosis, but an improved ability to monitor a patient's withdrawal from anti-seizure medication, helping prevent recurrence of a now controlled epilepsy syndrome.

In summary, many advances have contributed toward the great leaps forward this field, but the ability to see and model the actual neuronal events as they occur in real time to such a fine spatial and temporal resolution has no doubt been Neuroscience's crowning achievement of the past 20 years.

References

(1) Richardson, M. P. (2003). "Epilepsy and surgical mapping." British Medical Bulliten 65(1): 179-192.

(2) Westbrook Gary L. Seizures And Epilepsy p.911 In: Eric R. Kandell, James H. Schwartz, Thomas M. Jessell. Principles Of Neural Science, McGraw Hill USA. 2000

(3) Commission on Classification and Terminology of the ILAE. Proposal for classification of epilepsies and epileptic syndromes. Epilepsia 1989;30: 389-399

(4) Westbrook Gary L. Seizures And Epilepsy p.917 In: Eric R. Kandell, James H. Schwartz, Thomas M. Jessell. Principles Of Neural Science, McGraw Hill USA. 2000

(5) Lothman EW. 1992. Basic mechanisms Of The Epilepsies. Curr Opin Neurol Neurosurg 5:216-223

(6) Prince DA, Connors BW. 1986. Mechanisms of interictal epileptogenisis. Adv Neurol 44:275-299

(7)George Lee Morris III, W. M. Mueller, F. Z. Yetkin, V. M. Haughton, T. A. Hammeke, S. Swanson, S. M. Rao, A. Jesmanowicz, L. D. Estkowski, P. A. Bandettini, E. C. Wong, J. S. Hyde, Functional Magnetic Resonance Imaging in Partial Epilepsy, Epilepsia 1994 35:6 1194

(8) K. Krakow , F. G. Woermann , M. R. Symms , P. J. Allen , L. Lemieux , G. J. Barker , J. S. Duncan , and D. R. Fish EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures Brain 122: 1679-1688

(9) Sally F. Barrington, Michael Koutroumanidis, Alexander Agathonikou, Paul K. Marsden, Colin D. Binnie, Charles E. Polkey, Michael N. Maisey, and Chrysostomos P. Panayiotopoulos. Clinical Value of ' 'Ictal' ' and the Routine Use of FDG-Positron Emission Tomography Simultaneous Scalp EEG Studies in Patients with Intractable Partial Epilepsies. Epilepsia, 39(7):753-766, 1998 Lippincott-Raven Publishers, Philadelphia

(10) Aubert-Broche, Berengere, Jannin, Pierre, Biraben, Arnaud, Bernard, Anne-Marie, Haegelen, Claire, Le Jeune, Florence Prigent, Gibaud, Bernard Evaluation of Methods to Detect Interhemispheric Asymmetry on Cerebral Perfusion SPECT: Application to Epilepsy J Nucl Med 2005 46: 707-713

(13) Connelly, A, Jackson, GD, Duncan, JS, King, MD, Gadian, D G Magnetic resonance spectroscopy in temporal lobe epilepsy Neurology 1994 44: 1411-1417

(14) Commission on the Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22: 489–501.

(15) Fritz E. Dreifuss. Classification of Epileptic Seizures In: Engel J, Pedley TA. (eds) Epilepsy: A Comprehensive Textbook. Philadelphia, PA: Lippincott Raven, 1998; p.517-533

(16) A Proposed Diagnostic Scheme For People With Epileptic Seizures And With Epilepsy: Report on the ILAE Task Force On Classification And Terminology http://www.ilae-epilepsy.org/Visitors/Centre/ctf/overview.cfm, last accessed 23rd March 2006

(17) Awad IA, Rosenfeld J, Ahl H, et al. Intractable epilepsy and structural lesions of the brain, mapping, resection strategies and seizure outcome. Epilepsia 1991;32:179-186

(18) T M Salmenpera, J S Duncan, Imaging In Epilepsy, J Neurol Neurosurg Psychiatry 2005;76(Suppl III):iii2–iii10. doi: 10.1136/jnnp.2005.075135

(19) Commission on Classification and Terminology of the ILAE. Proposal for classification of epilepsies and epileptic syndromes. Epilepsia 1989;30: 389-399

(20) Ajmone-Marsan C. Zivin LS. Factors related to he occurrence of typical paroxysmal abnormalities in the EEG records of epileptic patients. Epilepsia 1970; 11:361-381

(21) Fisher RS. Imitators of Epilepsy. New York: Desmos Publications, 1994

(22) Michael R. Sperling, Robert R. Clancy Ictal EEG In: Engel J, Pedley TA. (eds) Epilepsy: A Comprehensive Textbook. Philadelphia, PA: Lippincott Raven, 1998; p.851

(23) Gloor. P Electroencephalography and the role of intracerebral depth electrode recordings in the selection of patients for surgical treatment of epilepsy. In Porter R et al., eds. Advances in Epileptology, 15th Epilepsy International Symposium. New York: Raven Press, 1984; 433-437

(24) Haemaelaeinen, M. (1993). "Magnetoencephalography theory, instrumentation, and applications to noninvasive studies of the working human brain." Reviews of modern physics 65(2): 413.

(25) Carlos H. Muravchik, EEG/MEG Error Bounds for a Static Dipole Source with a Realistic Head Model, IEEE TRANSACTIONS ON SIGNAL PROCESSING, VOL. 49, NO. 3, MARCH 2001

(26) J.Vieth, H.Kober, P.Grummich, D.Ulbricht, C.Brigel, D.Claus1, P.B.C.Fenwick, Localization of the Epileptogenic Lesion by Focal Slow and Beta Wave MEG Activity, Biomedical Engineering (Berlin) 39(Suppl): 133-134, 1994

(27) John S. Ebersole EEG and MEG Dipole Source Modelling In: Engel J, Pedley TA. (eds) Epilepsy: A Comprehensive Textbook. Philadelphia, PA: Lippincott Raven, 1998; p.928

(28) Thomas R. Henry, Harry T Chugani. Positron Emission Tomography In: Engel J, Pedley TA. (eds) Epilepsy: A Comprehensive Textbook. Philadelphia, PA: Lippincott Raven, 1998; p.947-951

(29) Henry TR, Engel J Jr, Mazziotta JC. Clinical evaluation of intericatal fluorine-18-flourodeoxyglucose PET in partial epilepsy. J Nucl Med 1993b;34:1892-1898

(30) Max Wintermark, MD; Musa Sesay, MD; Emmanuel Barbier, PhD; Katalin Borbély, MD, PhD; William P. Dillon, MD; James D. Eastwood, MD; Thomas C. Glenn, MD; Cécile B. Grandin, MD, PhD; Salvador Pedraza, MD; Jean-François Soustiel, MD; Tadashi Nariai, MD, PhD; Greg Zaharchuk, MD, PhD; Jean-Marie Caillé, MD; Vincent Dousset, MD Howard Yonas, MD, Comparative Overview of Brain Perfusion Imaging Techniques, Stroke. 2005;36:e83, 2005

(31) John S. Duncan, Imaging and epilepsy, Brain (1997), 120, 339–37

(32) John S. Duncan, Imaging and epilepsy, Brain (1997), 120, 339–37

(33) Rang, Dale, Ritter, Moore, Pharmacology (5th Edition) Elsevier Ltd London 2003 p. 550-561

(34) Crawford PM. Epidemiology of intractable focal epilepsy. In: Oxbury JM, Polkey CE, Duchowny M. (eds) Intractable Focal Epilepsy. London: Harcourt, 2000; 25–40

(35) Luders H, Awad IA. Conceptual considerations. In: Luders H. (ed) Epilepsy Surgery. New York: Raven, 1992; 51–62

(36) K. Krakow , F. G. Woermann , M. R. Symms , P. J. Allen , L. Lemieux , G. J. Barker , J. S. Duncan , and D. R. Fish EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures Brain 122: 1679-1688.

(37) Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., andWeisskoff, R. M. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc. Natl. Acad. Sci. USA, 89: 5675–5679.

(38) Goodin DS, Aminoff MJ. Does the interictal EEG have a role in the diagnosis of epilepsy? Lancet 1984;1:837-838

(39) Aldenkamp AP, Bodde N. Behaviour, cognition and epilepsy. Acta Neurol Scand 2005: 112 (Suppl. 182): 19–25. _ BlackwellMunksgaard 2005.
(40) Schiessl I.; McLoughlin N. Optical imaging of the retinotopic organization of V1 in the common marmoset, NeuroImage, Volume 20, Number 3, November 2003, pp. 1857-1864(8)

(41) S.A. Masino, M.C. Kwon, Y.Dory, R.D. Frostig. Characterization of functional organization within rat barrel cortex using intrinsic signal optical imaging through a thinned skull, Proc. Natl. Acad. Sci. USA.
Vol. 90, pp. 9998-10002, November 1993