CHAPTER – 2- LITERATURE REVIEW

2.0 INTRODUCTION

The property of Nuclear Magnetic Resonance (NMR) was first described by Purcell and Bloch in 1946[1], a work for which they received the Nobel prize in 1952. Since then NMR has become a powerful tool in the analysis of chemical composition and structure. In 1973 Lautenberg and Mansfield used the principles of NMR to describe a technique for determining physical structure[5]. Since then Magnetic Resonance Imaging (MRI) has been used in many biomedical, chemical and engineering applications.

In this chapter the theoretical foundations, first of nuclear magnetic resonance and then magnetic resonance imaging are explained. Then the practical implementation of MRI is outlined, and an explanation of the artifacts’ that affect MR images given. The chapter ends with a discussion of the safety of MRI as a medical imaging modality. More detail is found in the standard texts on the subject, such as those by Abragamm, and Callaghan[8].

There are numerous variations on the basic MRI sequences described above. Several of them, notably interleaved EPI, are explained in other chapters. Other important sequences are outlined here.

Phase encoding on the fMRI image enables the information on the second dimension of the given image to be added to the one dimensional line profile. It is possible to extrapolate this procedure to the third dimension by introducing phase encoding along the z axis. Thus the 2D-FT technique is extended to a 3D-FT technique. All such volumar imaging sequences first involve the selection of a thick slice, or slab. Then phase encoding is applied in the z-direction and the y-direction, followed by a readout gradient in the x-direction, during which the FID is sampled. The assembled FID's are then subjected to a three dimensional Fourier transform yielding the volume image. Phase encoding can also be used in EPI instead of multi-slicing. The slice select gradient and RF pulse being replaced by a slab selective pulse and a phase encoding gradient along the z-axis.

Going even further, it is possible to acquire all the data to reconstruct a 3D volume from one FID, in the technique called Echo Volumar Imaging (EVI)[7]. This uses another blipped gradient in the z direction, as shown in Figure 2.1. The limitation in EVI is the need to switch the gradients fast enough to acquire all the data, before T$_2^*$ destroys the signal.
Often the main limitation in implementing fast imaging sequences such as EPI is switching the gradients at the fast rates required. A sequence which is similar to EPI, but slightly easier to implement is spiral imaging. This covers k-space in a spiral from the centre outwards, which requires sinusoidal gradients in x and y, increasing in amplitude with time. Such gradient waveforms are easier to produce than the gradients required for EPI. Spiral imaging also has the advantage of sampling the centre of k-space first, and so the low spatial frequencies, that affect the image the most are sampled first, when the signal has not been eroded by $T_2^*$. The pulse sequence diagram and coverage of k-space for spiral imaging are shown in Figure 2.1a[13].

In general imaging, the chemical shifts of the protons are ignored, and usually seen only as an artefact. However it is possible to image the chemical shifts, which gives not only spatial information but also spectral information. The technique, called Chemical Shift Imaging (CSI)
[13], treats the chemical shift as an extra imaging gradient in the fourth dimension. By introducing a variable delay between the excitation pulse and imaging gradients, the chemical shift ‘gradient’ will phase encode in this direction. Fourier transformation in this case gives the conventional NMR spectrum.

Finally, it is possible to image nuclei other than the proton. Sodium, Phosphorus and Carbon-13 have all been used to form biomedical images. In the case of Carbon-13, its low natural abundance makes it useful for tracer studies.

2.1 SAFETY CONSIDERATIONS IN FMRI

fMRI technique is used to image humans, it is important to keep the safety of the subjects or patients as a high priority. Since fMRI does not use any form of ionizing radiation, it is considerably safer than x-ray or radio-isotope techniques. However it is important, especially in a research setting, that the potential hazards of any new developments are carefully considered. In this section the major safety aspects are outlined.

2.1.1 STATIC MAGNETIC FIELDS

Most scanners used for fMRI use magnets with field strengths of anything from 0.1 T to 4 T. There are many opinions on the effect of magnetic fields on biological tissues, and many studies carried out on the subject, ranging from epidemiological human study to the investigation of the development of animal embryos in high fields. It is however concluded that there is no adverse biological effect from the static magnetic field used in fMRI [17]. Further experimentation will no doubt be carried out, and this view can be altered in the light of any new discoveries.

By far the more serious effect of the static magnetic field is the response of ferromagnetic objects to such fields. It is essential that no free ferromagnetic object is allowed near the magnet since the field will turn it into a projectile. In a laboratory setting this means that most tools, connectors, and other equipment to be used in the vicinity of the field must not be ferromagnetic. Subjects must be screened for objects like keys, pens, belts and other metal on clothing, as well as the possibility of surgical implants. Before scanning a subject it is also necessary to check that there would be no ill effects from exposure to the magnetic field. It is common to exclude people who are in the early stages of pregnancy, people who may have any kind of metal fragments in them, and those suffering from certain conditions such as epilepsy.
2.1.2 TIME VARYING MAGNETIC FIELDS

As well as the high static magnetic field used in MRI [22], it is possible that the two time varying fields, namely the gradients and the RF radiation, could affect the subject in the scanner.

The rapid switching of the field gradients, particularly in EPI, produces two safety concerns. Firstly there is the possibility of inducing voltages in tissue by Faraday's law. The current induced in a loop of tissue is dependent on the rate of change of the field (dB/dT), the conductivity of the tissue, and the cross section of the loop.

Calculations by Mansfield and Morris [9] show that for dB/dT = 1.0 Ts\(^{-1}\), the currents induced are of the order 1 mAcm\(^{-2}\). Cohen [8] reports of subjects experiencing mild neural stimulation at gradient field variations of 61 Ts\(^{-1}\) which is higher than the rates in normal use. It is wise however, if high switching rates are used, that subjects are warned of the possible effects, and monitored during the imaging.

A second safety concern with the gradients is that of acoustic noise levels. Since large currents are flowing through wires in a large magnetic field, a force is exerted on the wires. When the currents oscillate at audio frequencies, the resulting noise can be in excess of 100 dB. Subjects therefore must wear suitable ear protection during scanning, to reduce the noise to an acceptable level.

The heat that can be dissipated by Radio Frequency (RF) fields is a further source of concern. The currents induced in tissues by such fields are dissipated as heat. Although most tissue has adequate blood flow to carry the heat away, some anatomical regions such as the eye do not. It is sensible to keep the heating due to RF radiation to a minimum and the NRPB guidelines state that the body temperature or any mass of tissue should not raise by more than 1 degree centigrade. This is achieved by limiting the mean absorption rate in the whole body to 0.4 Wkg\(^{-1}\) and in any mass of tissue [24] to 4 Wkg\(^{-1}\).

**NOTE:** It is also essential that there are no conductive items touching the subject's skin, since the heating of such objects by the RF radiation can cause serious burns.

2.1.3 OTHER SAFETY CONSIDERATIONS

Claustrophobia, and other psychological problems, can prevent a subject from being able to enter the scanner, and should be screened for before attempting to scan. It is necessary to check the subject is fully informed as to the nature of the experiment and happy to proceed.
2.2 COMPARISON OF THE FUNCTIONAL BRAIN IMAGING MODALITIES

The brain imaging techniques that have been presented in this chapter all measure slightly different properties of the brain as it carries out cognitive tasks. Because of this the techniques should be seen as complementary rather than competitive. All of them have the potential to reveal much about the function of the brain and they will no doubt develop in clinical usefulness as more about the underlying mechanisms of each are understood, and the hardware becomes more available. A summary of the strengths and weaknesses of the techniques is presented in Table 2.1[15, 16, and 17].

<table>
<thead>
<tr>
<th>Technique</th>
<th>Resolution</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>SPECT</td>
<td>10 mm</td>
<td>Low cost</td>
<td>Invasive</td>
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<td></td>
<td></td>
<td>Available</td>
<td>Limited resolution</td>
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<tr>
<td>PET</td>
<td>5 mm</td>
<td>Sensitive</td>
<td>Invasive</td>
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<td></td>
<td></td>
<td>Good resolution</td>
<td>Very expensive</td>
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<td></td>
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<td>Metabolic studies</td>
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<td></td>
<td></td>
<td>Receptor mapping</td>
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<tr>
<td>EEG</td>
<td>poor</td>
<td>Very low cost</td>
<td>Not an imaging technique</td>
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<td></td>
<td></td>
<td>Sleep and operation monitoring</td>
<td></td>
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<tr>
<td>MEG</td>
<td>5 mm</td>
<td>High temporal resolution</td>
<td>Very Expensive</td>
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<td></td>
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<td>Limited resolution</td>
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<td>for deep structures</td>
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<td>fMRI</td>
<td>3 mm</td>
<td>Excellent resolution</td>
<td>Expensive</td>
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<td></td>
<td></td>
<td>Non-invasive</td>
<td>Limited to activation studies</td>
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Table 2.1 - Comparison of modalities for studying brain function

2.3 LITERATURE REVIEW ON BRAIN TUMOR

Reliable and fast detection/classification of brain cancer is of major technical and economical importance for the doctors. Common practices based on specialized techniques are slow, have low responsibility and possess a degree of subjectivity which is hard to quantify.
Machine Vision seems a suitable technique to automate. Computers are used successfully for detection & classification of brain cancer, segmentation of brain implementing the IP techniques like histogram equalization, thresholding, image enhancement, sharpening filters embedding with an artificial neural network(ANN/NN) approach [20].

Approximately 112,000 people in the United States are diagnosed each year with brain cancers. Of these, about 32,000 have primary brain tumors, meaning that the tumor actually began in the brain. The other 80,000 cases are tumors that had their origin as another form of cancer - such as breast or lung cancer - that metastasized to the brain. Approximately 20% of all primary brain tumors are benign and can be successfully treated with surgery and, in some cases, radiation. The number of malignant brain tumors appears to be increasing but for no clear reason. Brain tumors in the elderly are on the rise: the incidence of malignant brain tumors increases dramatically in people over age 65 [12, 18]. Primary brain tumors are the second most common cause of cancer death in the US among people ages 15 to 32; the fourth most common cause of cancer deaths among males aged 32 to 55; and the ninth most common cause of cancer death for all Caucasian Americans. Brain tumors also affect children and account for about 3,000 cases per year.

The great problem with brain tumors is that they are not well understood. Scientists do not know enough about what causes them although they currently believe that only about five per cent are inherited. The other 95% of brain tumors are believed to develop after genes have been altered or mutated. It takes many, many genetic mutations, however, to form a brain tumor. Exposure to certain chemical and physical substances and to other environmental factors may play a role in the genetic changes leading to the development of brain tumors. Many people wonder if there is a relationship between the use of cellular phones and the development of brain tumors. While there is no scientific data yet to link the two, scientists have concerns about the possible relationship between exposure to electromagnetic fields and the development of cancer. There is no evidence yet regarding the role that viruses may play in the development of brain tumors [18, 19, 23]

Scientists at the U-M Comprehensive Cancer Center are testing the ability of diffusion magnetic resonance imaging to detect the earliest signs of a cancerous tumors response to treatment. Although the technology is commonly used to diagnose strokes, U-M researchers are the first to report its successful use in cancer treatment [8].
Over the past 10 years, a dramatic evolution has taken place in both the imaging and 
radio therapeutic treatment of cancers. In the past, clinicians treated tumors based on their 
anatomy; the focus now and in the future is on determining the biology of the tumor so that 
radiation therapy treatment plans can target individual characteristics within the tumor [9].

Wake Forest University Baptist Medical Center has been at the forefront of clinical 
imaging since the 1950s. With the creation of the Center for Biomolecular Imaging in early 
2002, Wake Forest joined the nation’s top ranks of academic centers in imaging research. “The 
Center was created in part to provide both basic science and clinical researchers with the imaging 
facilities needed for their ongoing investigations,” said Kerry Link, M.D., director of the Center. 
The remarkable advances in imaging technologies have had a major impact on clinical medicine 
as well as basic science and clinical research [11].

Anatomic imaging allows for the detection and location of tumors in tissues. Biologic 
imaging, a rapidly developing field, provides information on tumor biology, and may help 
identify when normal appearing tissues harbor cancer cells, how rapidly cancers are growing and 
tumors that lack in oxygen, an important determinant of a cancer’s sensitivity to radiation 
treatment.

The Radiation Oncology Department at Wake Forest Baptist will be one of the first in the 
country to have both CT/PET and MR spectroscopy modalities in its department for the purpose 
of treatment planning and research [12].

Being able to evaluate the individual biology of each tumor will allow clinicians to tailor 
or alter their therapy to effectively target each area of the tumor.

Since 1999, Wake Forest University Baptist Medical Center has offered patients a 
treatment option not available anywhere else in North Carolina — Gamma Knife® stereotactic 
radio surgery (SRS). Gamma Knife SRS is a non-surgical, non-invasive method of treating 
malignant and benign brain tumors as well as a number of other brain conditions including 
trigeminal neuralgia and vascular malformations [11, 12, and 13].

Researchers at the University of Connecticut Health Center (UCHC) are exploring 
applications of Maple in the interpretation of functional magnetic resonance imaging (fMRI) 
information for the early detection and characterization of small tumors. The UCHC team is 
demonstrating new ways that fMRI can be used as a superior way to detect and characterize 
small (2-2 mm), rapidly growing tumors. This research will enable doctors to use non-invasive
fMRI to identify and characterize human cancer tumors in their early stages of development and quantitatively follow the course of therapies. Till date, preliminary results have been done on mice. Clinical trials with human patients are anticipated in the near future [12].

The Duke Comprehensive Cancer Center is ranked 6th best cancer hospital in the nation in US News “Best Cancer Hospitals”. Dr. Allen Friedman - Allan Friedman, M.D., is an internationally recognized tumor and vascular neurosurgeon. He has a career-long interest in neuro-oncology, is responsible for over ninety percent of all tumor resections and biopsies conducted at Duke, and has written hundreds of articles on the neurosurgical management of brain tumors and vascular lesions. He is also head of the Laboratory of Neurosurgical Oncology and an associate chief of the Press Laboratory for Brain Tumor Research [19].

Automatic Brain Tumor and Edema Recognition and Segmentation in fMRI-the task in this problem is to automatically detect the presence of tumors in MR images of the brain, and segment the abnormal pixels from the normal pixels. Traditionally, the task has tried to segment the metabolically active 'enhancing' area of the tumor, which appears hyper-intense in T1 weighted images after the injection of gadolinium. Several recent methods have focused on additionally segmenting non-enhancing regions, as well as tumors that may only partially enhance or do not enhance at all. Several recent methods have also focused on the related task of segmenting edema (swelling) associated with tumors [15].

A Simple Method for Detecting Tumor in T2-Weighted fMRI Brain Images -the objective of this thesis is to present a decision support system which uses a computer-based procedure to detect tumor blocks or lesions in digitized medical images in the early stages. The authors G Vijay Kumar and Dr. G V Raju [25,26] developed a simple method with a low computation effort to detect tumors on T2-weighted Functional Magnetic Resonance Imaging (fMRI) brain images, focusing on the connection between the spatial pixel value and tumor properties.

2.3.1 LIMITATIONS

This thesis work implements Early Brain Cancer Detection using Blind Source Separation (BSS) Techniques [25,26]. The implemented system gives less accuracy under high intensity background of fMRI images. Feature extraction & neuro-classification is the basis of the early brain cancer detection by characterizing fMRI images into different classes. The images
in this study are acquired from fMRI samples. The project is not tested on mixture of different types of images. The training data contains less number of images, which is not sufficient. It is necessary to collect more images (data) to increase the training data set and ensure proper training. Experiments proposed in the thesis are performed on a small patient set and it is therefore essential to expand the training database [17].

2.3.2 BRAIN CANCER CHARACTERISTICS

Glial cell tumors or Gliomas

There are two types of cells that make up the nervous system: neurons and neuroglia. Neurons send and receive nerve messages. Neuroglia, otherwise known as glial cells, often surround the neurons. Glial cells play a supportive role by nourishing, protecting and supporting neurons. There are six kinds of glial cells; oligodendrocytes, astrocytes, ependymal cells, Schwann cells, microglia, and satellite cells.

A brain tumor that develops from glial cells is called a glioma. About half of all primary brain tumors and one-fifth of all primary spinal cord tumors form from glial cells. Gliomas tend to grow in the cerebral hemispheres, but may also occur in the brain stem, optic nerves, spinal cord, and cerebellum. Gliomas are divided into subgroups depending on the origin of the glial cells. The most common type of glioma is an astrocytoma.

Astrocytoma

An astrocytoma develops from star-shaped glial cells (astrocytes) that support nerve cells. These tumors can be located anywhere in the brain, but the most common location is in the frontal lobe. Astrocytomas are the most common primary CNS tumor.

The physician, usually the neurosurgeon or neuro-oncologist, will discuss the type and location of an astrocytoma. The pathologist will assign it a grade. Astrocytomas are generally classified as low or high grade. Low-grade astrocytomas are slow growing. High-grade astrocytomas (grades three and four) grow more quickly. The main tumor type is listed for each grade. There are additional tumor types in each of these grades.

The WHO classification divides astrocytomas into four grades:

• Grade I, Pilocytic Astrocytoma
• Grade II, Low-Grade Astrocytoma
• Grade III, Anaplastic Astrocytoma
• Grade IV, Glioblastoma Multiforme (GBM or Glioblastoma).

2.4 BLIND SOURCE SEPARATION REVIEW

2.4.1 INTRODUCTION

Many source separation algorithms have been proposed in the literature, although none of them can sufficiently separate a target speaker from a reverberant mixture well enough to restore automatic speech recognition performance to its levels in quiet. This section describes some of these approaches and their performance and limitations in reverberation. The broad categories of systems described include microphone arrays, blind source separation and independent component analysis, which typically utilize more than two microphones; monaural separators and strong prior models of speech and robust speech recognition, which typically utilize only a single microphone; and finally binaural computational auditory scene analysis (CASA) systems, which are most similar to this work, involving a pair of microphones [15].

2.4.2 BLIND SOURCE SEPARATION (BSS)

Adaptive beamformers can be considered one class of solutions to the general problem of blind source separation (BSS) (Douglas, Pedersen et al.) [16]. The term “blind” serves to emphasize that neither the signals nor the mixing system (array parameters) are known by the separator. While beamforming focuses on the spatial qualities of the sources, independent component analysis (ICA) is another class of BSS algorithms that take advantage of the statistical properties of the signals themselves.

ICA was first proposed by Bell and Sejnowski [17], who focused on solutions to the instantaneous mixing problem, i.e. the measured signals were assumed to be noiseless linear combinations of a set of input signals. By optimizing appropriate signal-dependent criteria, the original signals could be unmixed from one another up to an arbitrary scaling and permutation of the sources. Many overviews of ICA have been written, the interested reader is referred to (Hyvarinen, Choi et al.)[18].

Because acoustic mixtures tend not to be instantaneous, but include delays and convolutions with spatial impulse responses, Smaragdis [17] proposed applying ICA to individual frequency bands of spectrograms instead of directly in the time domain. Thus any delays or convolutions that were shorter than the window used to calculate the spectrogram were transformed into phase modifications and instantaneous ICA could still be applied. Solving a
separate ICA problem in each frequency leads to the so-called source permutation problem, in which the wideband signals must be reconstructed by combining the appropriate narrowband separations. Many methods have been proposed to resolve this problem including comparing the envelopes of the separated narrowband signals (Ikeda and Murata)[20], using the spatial location of the narrowband signals (Saruwatari et al.) [17], and a combination of the two (Sawada et al.)[21].

BSS has also been generalized to longer convolutions using a number of approaches. Pedersen et al. provide an excellent overview. Convolutive BSS systems take advantage of both spatial and signal-based properties of sound mixtures. One particular example of a convolutive ICA system is Triple-N ICA for Convolutive mixtures (TRINICON) (Buchner et al.). It takes advantage of the non-whiteness, non-stationarity, and non-Gaussianity of speech to estimate a convolutive unmixing system [17,24].

All of the microphone array and BSS techniques discussed so far can only separate sources from so-called over determined mixture conditions. This means that there are at least as many microphones as there are sources to be separated. They cannot separate sources from underdetermined mixtures where there are more sources than microphones. In this work, present methods designed for separating sources from underdetermined mixtures, as humans are able to do.

2.4.3 BINAURAL CASA SYSTEMS

Many systems have been proposed to take advantage of the cues that humans use to perform “auditory scene analysis” (Bregman [12]) in a process referred to as computational auditory scene analysis (CASA). While many CASA systems were monaural, a few have been binaural. These typically combine ideas of source localization with time-frequency masking, as our system does.

Perhaps the earliest was presented by Lyon [21], who proposed using the cross-correlation of the outputs of binaural cochlear filter banks to localize and separate sounds. The system was very computationally intensive at the time, and he was only able to run it on a single 200 ms example.

A similar system was proposed by Bodden [22] that additionally included a model of interaural level difference. After estimating the azimuth of each source, it derived a soft mask for separating the target source from interference. According to Brown and Palomaki [15] this
system did not perform well in reverberation because strong early reflections were classified as separate sources. An extension of this work that uses interaural coherence to distinguish between direct-path and reverberant sounds is described by Kollmeier et al. and Wittkop et al [23]. Aoki and Furuya [24] have extended these systems further to explicitly model the dependence of IPD and ILD on direction and weighting binaural cues by their reliability. (Liu et al., 2001; Palomaki et al., 2004 [15]) are in this vein as well.

### 2.4.4 IMAGE BASED BSS

Many scholars and researchers have been studying the problem of Blind Image Separation and numerous ways have been proposed to solve the problem. Recently attention has been drawn to Independent Component Analysis (ICA), which is a very important statistical tool for solving the BSS problem. As earlier said, the aforementioned applications involve convolutive mixtures of the sources. If they were mixed instantaneously, without any delay, solving the problem with ICA would have been far much easier. Instantaneous ICA is applied that would separate the sources (this will be shown later) although with the problem of scaling and permutation ambiguities. Due to filtering imposed on sources by their environments, difference between the sensors and propagation delays, what has been always observed in real world applications like the aforementioned applications on a convolved image. By extending the Blind Source Separation using Independent Components Analysis technique, the performance can be tested on the convolutive mixtures. There are three major approaches of solving the convolutive mixtures using ICA/BSS as enumerated in by Makino et al [25], which all have some advantages and disadvantages.

### 2.5 CONCLUSIONS

The literature relating to the research work in the field of fMRI imaging, Brain tumor detection and Blind source separation techniques is reviewed in this chapter. This survey covers the theoretical formulation and analysis as well as the aspects of practical fMRI imaging systems used to detect the brain tumors. From the study of the existing literature it has been observed that the Blood activity and cell flow related to de-oxy hemoglobin content cell that form the tumor at the early stages is not considered. Further, it is also observed that the imaging systems for detecting tumor at early stages based on the pixel activity has not been reported in the literature. The literature related to BSS is also discussed in detail. The main aim of this thesis is to develop
and design fMRI imaging system [26] that can detect the tumor at early stages by implementing BSS techniques.

2.6 REFERENCES

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26. G Vijay Kumar, Dr GV Raju, "Biological Early Brain Cancer Detection Using Artificial Neural Network", IJCSE Vol.2, No.8, 2721-2725, November, 2010