FUNCTIONAL BRAIN MAPPING BY
HIGH RESOLUTION ELECTROENCEPHALOGRAPHY
WITH DEBLURRING AND REALISTIC 3-D HEAD MODELS

by

SIMON MAN WAI AU YOUNG

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This thesis discusses the application of high resolution electroencephalography (HR-EEG) in human functional brain mapping. Clinically, mapping of brain function is important for epilepsy surgery. Routine electroencephalography (EEG) has been an important assessment tool for epileptic events and abnormal brain activity, whereas electrocorticography (ECoG) is the definitive clinical mapping tool to localize the epileptic focus. HR-EEG, with Deblurring™ and realistic head models, is a non-invasive method, and it may be able to provide more information during the pre-surgical evaluation than routine EEG. Deblurring™ is a signal enhancement technique to correct blur distortion of the scalp-recorded EEG signals. Realistic head models are constructed from subjects’ high resolution anatomic 3-D MRIs. This thesis examines the clinical potentials, benefits, and the validity of this method through a series of mapping studies on adult volunteers and two pediatric patients.

The results of the visual evoked potential (VEP) and functional magnetic resonance imaging (fMRI) study on adult volunteers showed that the deblurred results localized the brain region involved better than the scalp data. The deblurred topography did not match with the fMRI data in some subjects, which may be explained by the difference between surface mapping and 3-D activity mapping, and the volume conduction properties of EEG signals. The results of the SEP study on an adult volunteer showed that Deblurring™ improved the SEP peaks to become more focal and less variable than routine EEG or scalp HR-EEG. Patient studies allowed direct comparison of the deblurred results with the ECoG results. There was concordance between the deblurred and ECoG results in both SEP and seizure onset mapping.

The present HR-EEG with Deblurring™ technique has its shortcomings and limitations such that it is premature to conclude on the validity of Deblurring™ based on a small sample of subjects. However, the improvement of spatial resolution of the EEG data by higher density of electrodes and Deblurring™, plus the co-registration of the functional data on a realistic head model, may be able to provide extra information for placement of subdural grid before ECoG recording than clinical EEG data alone.
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INTRODUCTION TO HUMAN FUNCTIONAL BRAIN MAPPING

Brain mapping research attempts to identify distinguishable regions of the human brain in relation to their functional roles. Brain mapping researchers try to map brain regions responsible for basic physiological responses (e.g. visual, somatosensory, auditory, and motor functions) and cognitive functions (e.g. language, perception, and memory). The broad aim of human brain activity mapping is to provide realistic three-dimensional (3-D) maps and models of the structure, functions, connectivity, and pharmacology of the brain across developmental stages and health states (Pechura & Martin, 1991).

1.1 Rationale and Significance

This thesis discusses the application of a human functional brain mapping technique called high resolution electroencephalography (HR-EEG). HR-EEG, especially for application in the pediatric population, is still in its infancy. There is a need to investigate the clinical potential and the benefits of this brain mapping method as well as to validate the results. This thesis presents a part of the pilot study conducted at the Children’s Brain Mapping Centre (Vancouver, BC, Canada).

The unique features of the HR-EEG mapping technique, developed by Gevins and colleagues (Gevins, Le, Martin, Brickett, Desmond, & Reutter, 1994), and applied in our laboratory are:

1. the application of a denser array of scalp electrodes (84 or 128);
2. the co-registration of functional data on 3-D realistic head models; and
3. the use of Finite Element Deblurring™, a spatial enhancement technique, on the scalp-recorded potentials to correct distortion of the brain’s electrical signals.

The Finite Element Deblurring™ method refers to the spatial enhancement technique developed by Gevins and colleagues (Gevins, Le, Martin, Brickett, Desmond, & Reutter, 1994) and implemented in the Manscan® software (Beta 4.0 Version, SAM Technology, San Francisco, CA, USA). This proprietary technique will be short-termed as “Deblurring™” in the rest of the thesis.
The aims of this thesis are two fold:

1. to provide evidence of the benefits of applying the signal enhancement technique, Deblurring™, on the scalp-recorded EEG signals for mapping human cortical areas; and

2. to conduct within-person comparison of the deblurred signals with functional mapping results from other techniques to provide insight into the validity of Deblurring™.

Clinically, mapping of brain functions is important for epilepsy surgery. For patients with clearly defined seizure disorders that cannot be adequately controlled by medications, careful assessments of the type, frequency, and focality of epileptic events are important. Routine electroencephalography (EEG) has been an assessment tool for epileptic events and abnormal brain activity, whereas electrocorticography (ECoG) is the definitive clinical mapping tool to localize the epileptic focus. Doctors decide if surgical therapy (specifically, focal cortical resection or lobectomy) is feasible and appropriate based on the combination of case history, psychological testings and clinical examinations.

An ultimate advantage of HR-EEG mapping over ECoG is that it allows surgeons and the epilepsy care teams to gather more information about the epileptic focus and functional areas in a non-invasive way before opening the skull.

The scientific hypotheses for this thesis are:

1. Additional information can be provided by HR-EEG mapping with Deblurring™ for studying electrical activity of the brain, and

2. HR-EEG data correlate with other functional brain mapping results, such as functional magnetic resonance imaging (fMRI) and electrocorticography (ECoG).
1.2 Background

In order to study the connections of the functional pathways, scientists make use of research techniques to cause changes in the pathway and record the resultant changes along the pathway. These research techniques include chemical manipulation at the neuronal junctions, electrical manipulation within nerve fibres, and behavioural modification.

Direct electrical cortical stimulation is a common in-vivo neurophysiological technique in animal studies. These experimental animal studies involve extracellular electrical stimulation of specific neuron(s) on the cortical surface or within the cerebral cortex by means of stereotaxic apparatus, and recording of subsequent changes in electrical activity in other neurons (e.g. Au-Young, Shen, & Yang, 1999). Electrical manipulation of neurons is a more direct and specific method of changing the firing rate or pattern of neurons.

The direct human electrical cortical stimulation technique was developed in the 1930s by Dr. W. Penfield, a Canadian neurosurgeon, to determine intra-operatively cortical regions that perform important functions to spare those tissues during removal of a seizure focus. Penfield and Boldrey (1937) observed functional responses and obtained subjects’ report of changes in sensation and feeling with direct stimulation of the cortical surface by electrodes, especially in the Rolandic region (i.e. pre- and post-central areas). Classical diagrams of the human cortical areas responsible for motor and somatosensory functions of various parts of the body were made as a result of these intra-operative observations (Penfield and Rasmussen, 1950). These diagrams are called the motor homunculus and the sensory homunculus (Figure 1). Direct stimulation of the human cortical surface continues to play an important role in the operating room for pre-surgical mapping in epileptic focus and tumour resections today (Lesser, Lüders, Klem, Dinner, & Morris et al., 1987).
FIGURE 1  (A) The Motor Homunculus and (B) the Sensory Homunculus
Another human cortical mapping technique records evoked responses at the cortical surface (i.e. ECoG recording) elicited by stimuli applied to sensory receptors and nerve fibres (Goldring, 1978). This method is the opposite to Penfield’s method: recording is done at the cortical surface and stimulation is done at the peripheral nerves or receptors. Usually in the operating room, a combination of the electrical stimulation method and the ECoG evoked response recording method is used. For example, to map the central sulcus, body movement, such as finger twitching, can be observed during cortical stimulation at sites anterior to the central sulcus (i.e. Penfield’s method) and somatosensory evoked cortical responses recorded by ECoG during hand stimulation at sites primarily posterior to the central sulcus (i.e. Goldring’s method). By doing so, the area surrounding the central sulcus is studied more thoroughly. Such functional data are useful for evaluating whether resection is possible without producing significant functional damage, and for delineating location(s) for resection.

Intra-operative localization results, together with the overall clinical history from pre-surgical functional mapping, psychological testing, anatomical scans, and the prospects of a good surgical outcome, are important factors to determine locations and extent of resection area in excisional brain surgery.

These intra-operative mapping techniques are the clinical standards for brain functional region localization. Direct cortical stimulation and ECoG are clearly not suitable for studying brain functions in the non-surgical population due to their invasiveness. Therefore, non-invasive techniques have been developed in the past 30 years to provide tools to conduct functional brain mapping research, especially in the cognitive psychological research arena (Papanicolaou, Rogers, & Baumann, 1991; Perrine, Uysal, Dogali, Luciano, & Devinsky, 1993; Posner, 1993; Sarter, Berntson, & Cacioppo, 1996).

Transcranial magnetic stimulation (TMS) allows stimulation of the cortical neurons through the skull and scalp. Non-invasive brain activity recording techniques include EEG, magnetoencephalography (MEG), single photon emission computed tomography (SPECT), positron emission tomography (PET),
and functional magnetic resonance imaging (fMRI). These methods can record brain activation in subjects or patients during visual, somatosensory, and auditory stimulation; and performance of cognitive tasks involving language, perception, memory, and movement. Various combinations of stimulation and recording methods allow measurement of brain activation in more subjects over many situations. The analytical techniques within each recording modality allow extraction of brain signals related to the stimuli and determination of the spatial distribution of the recorded signals for non-invasive functional brain mapping.
1.3 **Overviews of Methods**

The human functional mapping techniques described here are widely used in research laboratories throughout the world. Newer techniques, such as optical intrinsic signal imaging, are being developed for human studies and will not be discussed here (Haglund, Ojemann, & Hochman, 1992; Hodge, Stevens, Newman, Merola, & Chu, 1997).

1.3.1 **Functional Mapping by Electromagnetic Activity Recording**

There are two non-invasive functional mapping techniques which record directly collective activity of many neurons from the exterior of the scalp. EEG records the electrical activity of cortical neurons while MEG records the electromagnetic activity of cortical neurons.

1.3.1.a **Electroencephalography (EEG)**

EEG allows for the differentiation between various behavioural states with changes in the electrical activity of the cerebral cortex. EEG measures extracellular volume currents. Event-related potential and evoked potential recordings, which are specific applications of EEG and will be discussed in Section 2.3.2, collect and extract components of brain electrical activity related to specific tasks, such as language, reading and memory; and specific functional systems, such as vision, hearing, touch, and motion. Brain electrical activity is recorded by electrodes applied to the scalp surface arranged in a standardized array system called the 10-20 System (Jasper, 1958). Routine EEG requires 20 electrodes for each recording. The conduction of the electrical potentials from the biological tissues to the recording electrodes is accomplished by using electrolytes, principally sodium chloride gel or paste. The electrical activity is then amplified and measured by an EEG machine. The localization of EEG activity and mapping of brain functions involves analyzing the distribution and amplitude of electrical activity recorded by the electrodes over the scalp (Rush, 1969). The dipole localization method (DLM) has been
developed to compute the source generating the recorded EEG activity (Fender, 1987).

One problem of measuring brain activity by EEG is that the skull and the scalp can act as barrier to the brain electrical signals and distort scalp-measured EEG signals. (Cuffin & Cohen, 1979). ECoG records brain electrical signals on the cortical surface and, therefore, brain activity is recorded without being filtered by the resistivity of the skull. Attempts to improve EEG-recorded brain activity to model real cortical potentials are important steps to expand the application of EEG for mapping human brain functions (Cuffin, 1990 & 1996; Gevins, Le, Leong, McEvoy, & Smith, 1999; Gevins, Leong, Smith, Le, & Du, 1995). Furthermore, electrodes are placed on the scalp surface which make EEG study of deep brain tissues harder to carry out due to long distance from the source(s). The detection of signals from the deep tissues can be harder due to lower signal amplitude and more mixing with background noise before being picked up by the electrodes. Special electrodes, such as nasopharyngeal or sphenoidal electrodes, can be used to record medial temporal activity, but these electrodes are not entirely non-invasive and are for clinical use only. A limitation of conventional EEG mapping is that it has low spatial resolution. This is due in part to the relatively low density of sampling points (i.e. sparse number of recording sites) used in routine EEG studies. HR-EEG tries to improve this limitation by sampling at more electrode sites simultaneously (Nunez, Silberstein, Cadusch, & Wijesinghe, 1993). However, equipment to handle simultaneous recording up to 256 channels is available only in EEG research laboratories.

A big advantage of mapping human functions by EEG is that it has temporal resolution in the milli-second range. This is important for studying the temporal characteristics and dynamics of the cortical activities (Gevins, Smith, Le, Leong, & Bennett et al., 1996). Moreover, EEG facilities are widely available in clinics and hospitals. EEG recording can be done in a more natural environment outside the laboratory if a mobile EEG system is used. Many other mapping methods involve large stationary recording machines, a special recording environment, and/or immobilization of the subject’s
head position.

1.3.1.3 Magnetoencephalography (MEG)

MEG, similar to EEG, measures neuronal activity directly. Instead of measuring brain electrical activity, electromagnetic activity is recorded. Therefore, MEG primarily measures intracellular currents in the cortex which generate an associated magnetic field according to the right-hand rule of physics. The magnetic field is measured by sensors arranged in a fixed array which cover part or all of the subject’s head. The brain’s magnetic fields are difficult to measure because they are very weak, in the femtoTesla or $10^{-15}$ Tesla range. In comparison, the earth’s magnetic field is one billion times larger than a typical cerebral signal. Therefore, extremely sensitive magnetic detectors known as SQUIDs (Superconducting Quantum Interference Devices) are needed to detect the cortical magnetic fields. Liquid helium, which has a temperature of -269 degrees C, is required to maintain the sensors at a superconductive state. Moreover, a special magnetically shielded metal room is usually required to minimize vibrations in the recording environment and the effect of the earth’s magnetic field. However, successful attempts to conduct MEG recording without magnetic shielding by high order gradiometers have been reported (Weinberg, Brickett, Vrba, Fife, and Burbank, 1984). The distribution and amplitude of magnetic activity is analyzed to localize the cortical activation region. Magnetic source imaging (MSI) technique, comparable to the DLM for EEG, can be used to compute the source producing the magnetic activity during a task, which can then be co-registered with anatomic MRI data.

Because an MEG recording uses more channels (37 to 142 channels) than a routine EEG recording and MEG signals are not distorted by the skull and scalp like EEG, raw MEG data have higher spatial resolution and simpler steps for localization of activity. MEG has a temporal resolution similar to EEG. MEG recording sensors do not need contact with the skin. Consequently, the time for preparing a MEG recording can be much shorter than a similar EEG recording. Many studies show that MEG and
EEG yield complementary results (Baumgartner, 1994; Cohen, Cuffin, Yunokuchi, Maniewski, & Purcell et al., 1990; Stefan, Schuler, Abraham-Fuchs, Schneider, & Gebhardt et al., 1994); however, the combination of MEG and EEG have been shown to increase the localization certainty (Fuchs, Wagner, Wischmann, Kohler, & Theissen et al., 1998; Sutherling, Levesque, Crandall, & Barth, 1991; Wood, Cohen, Cuffin, Yarita, & Allison et al., 1985). MEG equipment is more expensive than EEG equipment because of the higher cost and maintenance of the superconductive sensors than EEG electrodes. During MEG recording, the subject’s head needs to be fixed so that its distance from the sensors is not changed during the whole length of the experiment. Seizures with motor symptoms, such as tonic-clonic seizures, may present problems for a MEG recording. There are fewer MEG facilities. Hence, MEG is less used for pre-surgical evaluation and seizure recording internationally.

1.3.2 Functional Neuroimaging by Nuclear Medicine

The mapping techniques discussed so far directly measure activity of the cortical neurons. There are functional brain mapping techniques which measure cortical activation indirectly through cerebral mechanisms coupled with neuronal activity.

PET and SPECT are two functional brain mapping techniques that use radioactive-labelled compounds to track biochemical and physiological mechanisms. These methods indicate local brain activation by measuring changes in blood flow and volume, oxygen utilization, and/or neurotransmitter synthesis in specific brain regions. Brain areas that are more activated have higher metabolism and need larger amounts of blood to carry nutrients and oxygen to them (i.e. increase blood flow and volume) (Fox & Raichle, 1986). However, the neuronal and metabolic interactions are complex. For example, blood flow increase associated with increased neuronal activity has been shown not to change in proportion to oxygen utilization (Fox, Raichle, Mintun, & Dence, 1989). The exact relationship between vascular control and neuronal activity is incompletely understood.
**1.3.2.a Positron Emission Tomography (PET)**

PET and SPECT differ from each other in the way brain metabolism is measured and counted. PET measures the positron-emitting isotopes incorporated in biological compounds, such as water (as $\text{H}_2\text{H}^{15}\text{O}$), for measurement of regional cerebral blood flow; and deoxyglucose (as $[^{18}\text{F}]-\text{DG}$), for assessment of glucose metabolism. During the decay of an isotope, such as $^{15}\text{O}$, a positron is produced which can combine with an electron within a distance of a few millimetres because of their charges. Subsequently, in annihilation, two photons are released and travel in opposite directions from each other. A PET scanner consists of sensors, called scintillators, to measure the interval between arrival of each annihilation photon to the detector, and software to calculate the location of disintegration of the positrons. Early PET systems consist of a single ring of detectors and a head support to fix the subject's head at the centre of the ring. Modern systems consist of multiple rings of detectors arranged in a stationary array to measure in three dimensions. PET has an in-plane resolution of 5mm and an axial resolution of less than 10mm (Thatcher, 1996).

The advantage of PET mapping is that it has relatively good spatial resolution. However, the maintenance of a PET research program is expensive and demanding because an on-site cyclotron is needed to produce short-lived isotopes. The temporal resolution of PET is also relatively low, about 10sec.

**1.3.2.b Single Photon Emission Computed Tomography (SPECT)**

SPECT localizes human brain activation by measuring the quantity of single photon radiation (i.e. gamma rays) by an orbiting gamma camera. Tracers, such as $^{99m}\text{Tc}$-hexamethylpropyleneamineoxime (HMPAO or Examatazine), produce the photon flux for SPECT imaging. The tracers distribute according to regional blood flow and trap in brain tissues. Thus, images taken by a SPECT camera show the area of brain activation as an area of increased tracer uptake due to locally increased blood flow.
Because SPECT technology is cheaper than PET technology and slower decaying radio-pharmaceuticals are used, more SPECT facilities are available. Thus, SPECT imaging is used widely for clinical purpose. Although SPECT has a spatial resolution of about 10mm, and a temporal resolution of about 10sec, SPECT imaging is affected by the scatter and attenuation problems of the photons as they pass through tissues. This reduces the precision of localization and quantification of physiological changes as compared to PET, which has more advanced recording sensors and analytic algorithms to correct scattering problems for each pair of annihilation photons.

1.3.3 Functional Neuroimaging by Magnetic Resonance Imaging (fMRI)

fMRI is a relatively new technique for measuring functional changes in the brain. It was developed in the early 1990s (Kwong, Belliveau, Chester, Goldberg, & Weisskoff et al., 1992; Ogawa, Tank, Menon, Ellerman, & Kim et al., 1992). This technique, like PET and SPECT, relies on the secondary hemodynamic effects as an indication of the activation state of different brain regions. However, this technique uses no radioactive markers. Instead, it measures the intrinsic signals that occur as a result of differential concentrations of deoxyhemoglobin in venous blood in brain regions with increased neuronal activity. fMRI is based on the principle that the magnetic resonance (MR) signal changes in response to changes in the magnetic character of the intravascular contents. Since deoxygenated hemoglobin is more paramagnetic than oxygenated hemoglobin, it can act as a non-invasive, endogenous contrast agent. In activated brain regions, an elevation of cerebral blood flow and volume lowers the relative concentration of deoxyhemoglobin. This effect of blood oxygenation on MR image intensity is termed the "blood oxygenation level dependent" (BOLD) contrast level (Ogawa, Lee, Nayak, & Glynn, 1990). The decrease of the paramagnetic agent concentration results in increased signal intensity in a T2*-weighted MR image (a specific type of MR images), such that the activated areas are whiter than the rest of the brain. By doing statistics on the pixels of MR images, the MR image intensity,
which reflects deoxyhemoglobin concentration and subsequently neural activation level, can be compared to the image intensity for baseline states. Therefore, BOLD relies on a physiological phenomenon during brain activation to produce contrast. However, there is no direct measure of physiological parameters, like PET and SPECT, which can measure absolute blood flow with radioactive tracers. The exact relationship between the T2* relaxation rate (i.e. T2 MR image pixel intensity) and cerebral blood flow is not yet clarified (Eden, VanMeter, Rumsey, Maisog, Wood, & Zeffiro, 1996). There is a fMRI signal lag of 4-10sec between the neuronal changes and the effect of the hemodynamic response. This limits the temporal resolution of fMRI because the latency of the hemodynamic response time may not be the same for all areas of the brain (Menon, Gati, Goodyear, Luknowsky, & Thomas, 1998).

MRI scanners operating at field strengths of 1.0 Tesla or more can produce excellent structural images and, with modern gradients, can have very fast imaging sequences for generating enough snapshots during the functional tasks to demonstrate brain activation. Since most clinical MR (1.5T) scanners can be adapted for functional studies, fMRI is a more affordable and available method than PET. Moreover, acquisition of both anatomical and functional data can be collected within a single scanner, which makes registration of the functional data to the anatomy easier to do. The spatial resolution for fMRI is dependent on the magnetic strength (about 3mm in-plane at 1.5T). People who are claustrophobic cannot stay comfortably inside the MR magnet during the experiment. Moreover, motion can create artifacts in the fMRI data. Because of the strong magnet in the MR environment, ferric metal cannot be brought near the magnet. Patients who have pacemakers, for example, cannot be scanned.

Table 1 summarizes the principles, advantages, and disadvantages of using the various functional brain mapping techniques discussed. Figure 2 compares the temporal and spatial resolution of the various functional brain mapping methods.
<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Time</th>
<th>Count</th>
<th>Bone Emission (PET)</th>
<th>Position Emission (SPECT)</th>
<th>Functional Magnetic Resonance Imaging (fMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available for detection in a few hours</td>
<td>10 sec</td>
<td>0.5 cm</td>
<td>Bone Emission (PET)</td>
<td>Position Emission (SPECT)</td>
<td>Functional Magnetic Resonance Imaging (fMRI)</td>
</tr>
<tr>
<td>Radioactive substance is used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signal changes occur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional imaging is possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI provides higher sensitivity and contrast</td>
<td></td>
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<td></td>
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<tr>
<td>MRI provides better spatial resolution</td>
<td></td>
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<tr>
<td>Finding the source is easier</td>
<td></td>
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<tr>
<td>perfusion is available</td>
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</table>

<table>
<thead>
<tr>
<th>Table 1: Overview of Functional Brain Mapping Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technique</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>PET</td>
</tr>
<tr>
<td>SPECT</td>
</tr>
<tr>
<td>fMRI</td>
</tr>
<tr>
<td>EEG</td>
</tr>
<tr>
<td>MEG</td>
</tr>
</tbody>
</table>
FIGURE 2  The Temporal and Spatial Resolutions of Functional Mapping Techniques

CHAPTER 2
INTRODUCTION TO ELECTROENCEPHALOGRAPHY

2.1 History

The first recording of human brain electrical activity dated back to 1929. Hans Berger, a German clinical neuropsychiatrist at the University of Jena, was the first to publish information about the cerebral origin of electrical activity of the human brain recorded from the skull, and coined the term "elektrenkephalogramm", which is the German equivalent of electroencephalogram or EEG. He was also the first to observe and describe many EEG features. He demonstrated that brain electrical activity consists more or less of a mixture of rhythmic, sinusoidal-like fluctuations in voltage, having a frequency of about 1 to 60Hz. In 1933, he was the first to record an epileptic seizure, which will be the abnormal EEG activity discussed in Chapter 5 (Swartz & Goldensohn, 1998).

2.2 Signal Generation

The human brain consists primarily of two specialized kinds of cells: neurons and glial cells. The glial processes intermingle and form a dense and highly complex matrix surrounding the neurons. The best estimate is that the human brain contains $10^{11}$ neurons.

A typical neuron has three morphologically defined regions: cell body, dendrites and axons. The cell body, or soma, is the metabolic centre of the neuron. The dendrites and axons are branches coming out of the cell body. In functional terms, the dendrites are short extensions of the cell body for receiving information, whereas the axons are the long fibres for carrying information to the synaptic terminals and subsequently transferring activity from one neuron to others by way of synaptic changes and neurotransmitters. The axon is tubular in shape with a diameter from 0.2 to 20μm. Transient electrical signals are conducted efficiently along axons by propagating as action potentials.
2.2.1 Neuronal Activity

The electrical activity of a neuron is generated by the special membrane properties of the nerve cells. In the resting state, the neural membrane is electrically polarized. This difference in voltage across the membrane originates from the selective permeability of the membrane to specific ions and maintenance of intra- and extra-cellular concentration of some ions by active mechanisms, such as active transport. Intracellularly, there is a higher concentration of potassium ions, whereas extracellularly, there is a higher concentration of sodium and chloride ions. Because the neuronal membrane is impermeable to large organic anions (negative ions) and there are an abundance of sodium ions extracellularly, the resting potential of the membrane is more negative intracellularly than extracellularly and is maintained at -40 to -90mV (Figure 3).

FIGURE 3 An Action Potential

![Diagram of an action potential](image)
The voltage-gated ionic channels, in particular those for sodium, potassium, and chloride are responsible for changing the membrane potentials. The two types of membrane potential fluctuations are the action potential and the synaptic potential. An action potential is a brief sequential polarization and re-polarization of membrane potential that propagates along an axon. An action potential starts when there is a decrease in negativity of the membrane potential of 20 to 30mV produced chemically by neurotransmitters or electrically, as in the electrical stimulation of a sensory nerve. The depolarization phase of an action potential then occurs as a result of the abrupt opening of the voltage-dependent sodium channels, which allows an influx of sodium ions to decrease the intracellular negativity of the membrane potential. The size of an action potential is about 100mV. Next, the gates of the potassium channels open and allow escape of potassium ions out of the neurons. This leads to the re-polarization of the resting membrane potential. An action potential differs from a synaptic potential by two properties. First, an action potential can propagate along the axons without diminishing amplitude. Second, an action potential spreads along the axons by a “wave” of depolarizations and re-polarizations.

Synaptic potentials are sometimes called miniature potentials. There are two types of synaptic potentials: excitatory post-synaptic potential (EPSP) and inhibitory post-synaptic potential (IPSP). EPSPs are usually about 5mV in size, and are formed when the sodium-inward current prevails. They can summate and cause sufficient depolarization to evoke an action potential. IPSPs, on the other hand, are current changes due to an influx of chloride ions or an outflow of potassium ions that hyperpolarize the cell membrane, and make an action potential harder to occur as a bigger initial change of the resting membrane potential is needed to start the depolarization stage of an action potential. The next section will show that current theory suggests that EEG waveforms represent summated field potentials set up by EPSPs and IPSPs from a large number of cortical neurons.
2.2.2 Cortical Structural and Functional Organization

In addition to interneurons, there are three main types of neurons in the cerebral cortex, namely the pyramidal neurons, the stellate neurons, and the spindle neurons. For scalp EEG electrodes to record brain activity, a relatively large area on the surface of the brain has to become either negative or positive. The size of the negativity or positivity must also be large enough in voltage (i.e. amplitude) to be measured as a deviation from the relative zero level. Large numbers of vertically orientated dipoles are therefore necessary for producing a sufficiently large field potential to be recorded extracellularly by scalp recording electrodes. The pyramidal cells are the main vertically orientated cells for forming the cortical layers (Figure 4). Layer I of the cortex consists mainly of the dendrites of the pyramidal cells whereas layers II and III contain the cell bodies. Changes to the membrane potential of these cells produce an extracellular current flow which are principal to field potential generation in the cortex and subsequently to EEG signals.

When an afferent fiber formed an excitatory synaptic contact at the superficial aspect of the apical dendrite, the stimulation of the afferent fiber causes an EPSP to be developed in the dendrite. As a result of the net influx of cations during depolarization of the post-synaptic membrane, a potential gradient exists along the neuronal membrane. The local excitation leads to an intracellular cation flow from the superficial surface to the deep layers to spread the EPSP electrotonically, and a counter extracellular current flow from the deep layers to the superficial surface. The extracellular current flow produces a field potential that has negative polarity at the surface (i.e. the “sink” for inflow of cations) and positive polarity in the deep layers (i.e. the “source” for outflow of cations). When an inhibitory synaptic contact is formed by an afferent fiber, an IPSP is formed after stimulation. This results in an extracellular current flow that is inverse in direction for one induced by a superficial EPSP. The field potential has positive polarity at the surface and negative polarity in the deep layers. An afferent fiber can also form an excitatory or inhibitory synaptic input in the deep parts of the perpendicular pyramidal neurons; for
example, directly with the cell body. A deep inhibitory synaptic input produces an extracellular current flow similar to a superficial excitatory input and evokes a negative field potential at the surface. A deep excitatory synaptic input causes a positive field potential at the surface (Speckmann, Elger, & Altrup, 1997).

When a large group of neighbouring neurons have post-synaptic potential changes at the same time, the EPSPs or IPSPs for the functional unit can summate and a measurable voltage change can be recorded over the scalp during EEG recording. Superficial EPSPs and deep IPSPs induce a negative field potential at the cortical surface and generate negative EEG signals. Superficial IPSPs and deep EPSPs induce a positive field potential at the cortical surface and generate positive EEG signals. Action potentials in the axons produce brief potential changes as compared to EEG waveforms. Thus, action potentials are believed to be an unlikely source of spontaneous EEG signals.

EEG records activity from many neurons rather than individual neurons. This is appropriate for understanding how the brain works because neighbouring neurons work together as a unit forming functional regions. For determining the functional anatomy, macro functional recording techniques, like EEG, are suitable.
FIGURE 4  The Human Cortical Structure

SUPERFICIAL SURFACE OF HUMAN FRONTAL CORTEX

PYRAMIDAL CELLS

(Ramón y Cajal's original drawings from History of the Nervous System of Man and Vertebrates, 1952.)
2.3 Electroencephalographic Signals

There are two general types of EEG signals, namely spontaneous signals and event-related potentials. Event-related potentials differ from spontaneous EEG signals by being associated with specific information processing tasks or stimuli.

2.3.1 Spontaneous Signals

EEG is an important clinical diagnostic tool for recording brain activity. Well-trained EEG technologists and electroencephalographers can distinguish normal and abnormal EEG patterns to make a diagnosis of the health state of brain activity of patients.

The normal EEG is characterized by rhythmic activity that is only occasionally punctuated by transient discharges. Some of the rhythms are alpha rhythm, mu rhythm, beta activity, theta rhythm, and delta activity. They are distinguished and classified along multiple dimensions, including location, frequency, amplitude, morphology, periodicity, and behavioural/functional correlates. Normal transient discharges are related to movement and sensation.

The alpha rhythm is one of the most prominent normal adult brain rhythms. It is fully present only when a subject is mentally inactive and awake with eyes closed. Its frequency varies from one person to another, ranging from 8-13 Hz. The highest amplitudes of the alpha rhythm can be measured at the occipital and parietal electrodes. Visual attentiveness causes significant decrease in alpha rhythm. The mu rhythm is a 7-11 Hz rhythm seen in 10% to 20% of EEG recordings. It shows maximal amplitude at central rather than occipital locations. High frequency activity around 40 Hz is often referred to as gamma activity. Beta activity has a frequency characteristic that is higher than 13 Hz. The amplitude of beta activity is 1 to 10 μV. The topography of beta activity is quite variable. Two common types are the frontal and the posterior beta rhythms. During drowsiness, alpha activity dissipates, and medium-amplitude theta (4-8 Hz, 10-50 μV) activity may become prominent. Delta activity is less than 4 Hz. It
is dominant in infants and is prevalent in deep stages of adult sleep.

The abnormal EEG includes rhythmic activity which differs from the normal rhythms by location, frequency, amplitude, morphology, and behavioural/functional correlates. For example, prominent delta activity in the EEG of an awake adult is a significantly abnormal finding. Abnormal EEG also includes transient discharges, such as spikes, sharps, and slow waves. Specific abnormal EEG discharges for epilepsy will be discussed in Chapter 5.

2.3.2 Event-related potentials

Event-related potentials (ERPs) are neuronal activities which are elicited by a physical task, or a psychological or perceptual event. The changes in voltage ('potential') can occur before, during or after a task or an event ('event-related') (Picton, 1988). ERP researchers are interested in finding the relationships between events in a cognitive task or an information processing function and their elicited voltage changes. Potentials related to motor tasks (e.g. readiness potential and contingent negative variation), stimulus discrimination and attention (e.g. P300) are examples of ERPs.

2.3.2a Evoked Potentials

Evoked potentials (EPs) are ERPs that occur following an external physical stimulus, which is used to trigger a sensory pathway. EP researchers concentrate on studying the effect of sensory stimuli (e.g. rate, intensity, and mode) on the elicited responses and the difference in those responses between different populations of subjects. Sensory stimulation produces electrical responses in the relay stations of the sensory pathways and cortical receiving areas. EPs are very low amplitude responses superimposed on normal EEG activity, such as the spontaneous EEG patterns discussed before. The relatively low signal-to-noise (S/N) ratio makes the measurement of the EPs difficult. Two types of evoked potentials were studied in this thesis: visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs).
Because EPs are just special EEG data, they can be collected and analyzed by using the HR-EEG protocol.

2.3.2.b Transient and Steady-State Evoked Potentials

EPs elicited by one kind of stimulus can further be classified, based on the stimulus presentation rate, into two subtypes. When stimuli are presented to the subject infrequently, a break occurs between two stimuli for neurons in the brain response areas to return to the resting state before responding to the second stimulus. This type of evoked potential is called a transient EP. Each raw EP (i.e. 1 trial or sweep) represents the resting state before the stimulation, the response to the stimulus, and the return of the potential to the resting state. It is assumed that the EP triggered by one stimulus does not affect and is not affected by EPs triggered by other stimuli.

When the stimuli are presented close to each other to the subjects such that there is a sustained response in the brain response areas, the elicited response is called a steady-state EP. A steady-state EP is assumed to be constant in amplitude and phase. Because the difference between the two types of EPs is the rate of presentation, and not the kind of stimulus, the brain response area should be similar (Regan, 1982). The advantage of collecting steady-state EPs for electrophysiological brain mapping is that less time is required to collect enough trials to produce an averaged signal with a satisfactory S/N ratio. However, it is not possible to distinguish the temporal relationships between different activated areas as the evoked peaks or components of the EPs are not entirely independent of each other. Steady-state EP protocols are considered by some researchers to be more appropriate to use for comparisons between regional cerebral blood flow activation studies (PET and fMRI) and EP studies. This is because the same stimuli can be strong activators of change in both cerebral blood flow and neuronal activity. Quantitative comparison between steady-state SEP data and fMRI data has previously been demonstrated with steady-state somatosensory stimulation (Synder, 1992).
2.4 Basics of Electroencephalographic Recording

EEG recording is clinically performed at hospitals and clinics by certified EEG technologists. Interpretation of the EEG data is performed by electroencephalographers, who are usually neurologists with special EEG training.

2.4.1 Electrode Placement: the 10-20 System

The 10-20 International System uses standard landmarks on the skull to measure positions for electrode placement (Jasper, 1958; Steinmetz, Furst, & Meyer, 1989). This system allows full coverage of the head. The anterior-posterior (A-P) measurements are based on the distance between the nasion and the inion measured along the midline over the vertex. The nasion is the indentation at the top of the nose, level with the eyes. The inion is the bony lump along the midline at the base of the skull at the back of the head (Regan, 1989). The lateral measurements are based on the distance between the preauricular points. The preauricular points are where the external ear flaps merge with the scalp on the face side (Regan, 1989). All electrodes are then placed in reference to the distances between these landmarks.

This 10-20 system can be used for both infants and adults. The term, “10-20”, refers to the distance between two neighbouring electrodes which equals to 10% or 20% of the measurements between the reference landmarks. For HR-EEG, an extended 10-20 system is used (Guideline, 1994; Sharbrough, Chatrian, Lesser, Lüders, & Nuwer et al., 1991). Often, this system is called the 10-10 system. As electrodes are spaced closer together, the distance between two neighbouring electrodes becomes 10% of the measurements between the reference landmarks.

Electrodes at different locations of the head are named systematically for identification purposes. The initial capital letters refer to the anterior-posterior placement of the electrodes, and correspond to the underlying brain structures. From anterior to posterior, the “lines” of electrodes in a 128-channel electrode system are “FP” (frontal pole), “AF” (anterior-frontal), ”F” (frontal), ”FC” (frontal-central), “C”
(central), "CP" (central-parietal), "P" (parietal), "PO" (parietal-occipital), and "O" (occipital). The distance these lines of electrodes separates from each other is based on the measured distance between the nasion and the inion over the vertex in the midline.

Lateral distance is represented by numbers or the letter "z" in the electrode name. All electrodes along the midline end with the letter "z". All electrodes that line to the left of the midline carry odd numbers in their names, whereas the ones to the right have even numbers. The larger the numbers are, the further the electrodes lie away from the midline. The lateral measurement is based on the distance between the two preauricular points. Figure 5 shows the extended 10-20 International System of electrode placement for 84 electrodes.
FIGURE 5  The Extended 10-20 International System of Electrode Placement (84-Channel Layout)
2.4.2 **Recording System**

An EEG recording system consists of three main parts: input device, data processor, and data output. The data processor of an EEG recording system consists of amplifiers for multiplying the EEG signals for output, and filters for removing noise from the recorded signals. In the past, amplified EEG data were written out in paper form, i.e. as electroencephalograms. The electrical signals recorded are converted into mechanical signals; thus, pens in the paper EEG machine draw out the waveforms. The bigger the electrical action, the more a pen deviates from baseline. A modern EEG recording system is a computer workstation where EEG data are collected and saved in digital form. Many of these systems also include software for processing the recorded data. Figure 6 shows the components of an advanced digital EEG recording system.
FIGURE 6 Components of a Modern Digital EEG Recording System

Test Subject / Patient → Evoked Potential Stimulator

Electrodes attached to patient's scalp → Electrode Board

Amplifiers & Recording Filters → A/D Conversion Component → Calibration Unit

Post-hoc Analysis e.g. filtering, FFT, averaging → Computer Processing Unit

A/D Conversion Component

Display

INPUT

OUTPUT
EEG data are first recorded by electrodes. EEG signals are recorded as a continuous measure of voltages in microvolts as a function of time, and are referred to as "analog" signals. The amplifiers and filters of the EEG system amplifies and cleans up the recorded EEG data so that they can be read by electroencephalographers. In a digital system, an analog-to-digital (A/D) converter changes these continuous signals into digital form for storage by sampling the data at regular intervals (i.e. at a fixed sampling rate) and represents them by a sequence of discrete numbers evenly spaced in time rather than as a continuous function (Figure 7). The step size of the discrete voltage levels in a particular EEG system affects the precision of the A/D conversion. Different EEG recording systems have different sampling rates and different numbers of voltage levels available. Eight-bit data sampled at 200Hz means that 200 sampling time points are collected in 1 second and the data are represented by $2^8$ discrete voltage levels. A high sampling rate and a large number of available voltage levels for the recorded voltage range, in general, results in higher precision of the digitized data (Figure 7). A digital EEG data set can also be thought of as a 3-D matrix where the electrode name distinguishes between different channels, the time axis specifies the temporal information of the dataset, and the amplitude shows the "quantity" of activity at that time point in microvolts ($\mu$V).
FIGURE 7  A/D Conversion of EEG Data

ANALOG DATA

DIGITAL DATA (Sampled at x Hz)
- POINTS ONLY

DIGITAL DATA (Sampled at 2x Hz)
- AND POINTS
2.4.3 Reference

EEG is a recording of the electrical activity of the brain; two electrodes are needed to be connected to each channel of an EEG recording system to complete a circuit. Data in each channel represent the difference in voltage between the two areas recorded by a pair of electrodes. The waveform and amplitude of EEG signals recorded generally depend on the locations of both electrodes. If a differential amplifier is used, the common-mode rejection does not allow changes common to both electrodes with respect to ground to appear at the amplifier output.

A montage, or a systemic arrangement of data from selected or all channels, is used for displaying data so that comparison between channels can be made. The two basic types of EEG montage are the monopolar and the bipolar systems. In the monopolar (or referential) montage, electrical activity measured at all electrodes is compared to one common reference electrode or the arithmetic mean of a set of common electrodes. If the common reference is inert to changes in cerebral electrical activity, then only the changes in the other electrodes are reflected in the voltage change in the EEG channels. This allows amplitude comparisons to be made between channels. One example of the referential montages is called the average potential reference, where voltages of all electrodes are included to calculate a mean voltage as reference. The average reference has the advantage of not favouring any particular electrode site. An ‘ideal’ average reference, suggested by Bertrand, Perrin, & Pernier (1985), is derived from an array of electrodes spaced regularly around the entire head rather than merely over the scalp. If the reference channel is really inert, the voltage in the reference channel is unaffected by the activity of the underlying brain activity. It is “monopolar” in the sense that only one electrode is “active” and shows changes related to the brain activity. However, there is “no location on the body that can be regarded as being at electrical infinity for all source configurations” (Regan, 1989, p.13). EEG and EP recordings from the active electrode are influenced by the reference electrode. The objective of choosing a good referential electrode is to minimize this effect on interpretation of the activity in the active electrode.
It is debatable in EEG and EP recordings what the best reference choice is because it is difficult to choose a reference site that is indifferent to the source of activity being measured. The underlying generators of the scalp EEG are large dipole layers of synchronized and somewhat aligned cortical neurons extending over large areas of the cortical surface (Nunez, 1981). The dimensions of the generators can be as large as tens of centimetres. Therefore, it is impossible to find a point on the head which can be at a distance far enough from the generators to be considered truly “inactive”. If a reference is placed distant to the head, such as the elbow or knee, the effective reference is actually located at the neck since there is no potential difference between the body and the neck. The neck is still not far enough from the generators to be considered “inactive”.

Bipolar montages do not allow amplitude comparison across channels as both electrodes in each channel are considered active and that the “reference” used in each channel can be different. These montages are useful for locating local electrical discharges by detecting polarity (or phase) reversals. The polarity of activity recorded by neighbouring pairs of electrodes in the bipolar montage can be opposite, signalling that the common electrode in the pair (e.g. “B” in pairs A-B and B-C) is likely to be involved in the recording of the activity. A closely spaced pair of electrodes is sensitive to the location and orientation of nearby sources, whereas a widely separated pair is comparatively insensitive to source location. The phase reversal method was developed for the localization of the central sulcus in the 1970s (Cedzich, Taniguchi, Schafer, & Schramm, 1996; Goldring, 1978; Goldring & Gregorie, 1984). This method is based on the fact that the electrical activity evoked by somatosensory stimulation is of one polarity in the sensory cortex, and of opposite polarity in the motor cortex. The phase for the evoked activity reverses across the central sulcus. Therefore, it is a non-invasive, practicable, and reliable method for intra-operative determination of the central sulcus when only a small portion of the brain is exposed. The success rate of SEP phase reversal mapping during epilepsy surgery and tumour surgery has been described to be over 90% (Cedzich et al., 1996; King and Schell, 1987).
2.4.4 Data Representations: Time and Frequency Domains

When EEG data are recorded, the x-axis represents time and the y-axis represents amplitude. This representation of data in the time domain is useful for displaying changes in brain activity over time. For example, Figure 8 shows changes in the spontaneous EEG waveforms due to eye movement.

EEG data can also be represented in the frequency domain. By the Fast Fourier Transform (FFT) algorithm, temporal data can be converted to spectral data. This representation allows the amount of activity in a given frequency or a frequency band present in the EEG data to be easily visualized. For example, when a segment of EEG data is converted to spectral data, a clear band of alpha activity at around 8Hz is observed (Figure 9).

Mathematically, any practical waveform can be described in either the time domain or the frequency domain. Time-domain data can be converted to frequency-domain data by means of the Fourier transform, whereas frequency-domain data can be converted to time-domain data by means of the inverse Fourier transform. One exact set of data can be described in the time-domain or the frequency-domain. The data are the same and carry the same amount of information; what is different is the way the data are described.
FIGURE 8  Eye-Related EEG Activity

FIGURE 9  Alpha Band Activity in Background EEG Recording
2.5 Electroencephalographic Activity Localization

The first published human electrophysiological brain maps were two-dimensional maps that summarized the EEG or EP data in a topographic format by representing the amplitude of each recording electrode in a gray-scale or simple colour scale (Duffy, 1982; Ueno & Matsuoka, 1976). Amplitudes for inter-electrode areas were computed by an interpolation algorithm. Both temporal and spectral data can be shown in a topographic map (Gregory & Wong, 1984; Nuwer, 1988a & b; Wong, 1990). With advances in computer technology, more detailed maps can be made. Presently, the topographic maps can be 3-D. The colour scale, used to represent amplitude, can contain more colours to represent smaller changes in amplitude. Advances have been made to improve interpolation algorithms to represent amplitude values between electrodes better.

One important use of topographic maps is to display electrophysiological activity distribution. For EEG, the potentials are recorded on the scalp whereas, for ECoG, the cortical surface. There are recordings done on the dura as well. Hence, the topographic maps carry information about the electrical activity at the surface boundary where the electrodes are placed. Localization of the peak response area can be derived from comparison of evoked response amplitudes recorded by different electrodes (Gevins et al., 1994) and/or observation of the location of phase reversal occurrence in the recorded potentials (Cedzich et al., 1996). However, the spread of electrical potentials via volume conduction prevents conclusions about the exact neuroanatomical location of an intracranial source to be drawn based on scalp-recorded electrical potentials alone. To localize the brain structures responsible for the electrical topographic patterns, i.e. source, mathematical source modelling techniques are needed. Two source estimation methods for electrical activity data are dipole localization method (DLM) and volume current imaging (Fender, 1987; Pascual-Marqui, Michel, & Lehmann, 1994).
Source localization is not an easy problem. A topographic map shows the scalp voltage distribution of the evoked potentials, which can be distant from the actual generating source due to volume conduction through the skull. Source localization methods try to infer the possible locations of the sources and face the “inverse problem”, which states that any given surface field can be generated by more than one source configuration, so that unique solutions are in general unobtainable (Helmholtz, 1853). Assumptions concerning the number, the location, the spatial extent of the dipole, the homogeneity and the geometry of the intracranial surface are needed to limit the solutions to physiologically meaningful ones. Hence, computation of the source by dipole localization method (DLM) carries an uncertainty in the estimation of the source (Scherg & Berg, 1991).

Co-registration of multimodal data helps to reduce the uncertainty of functional mapping results. Correlation of data from EEG with other techniques, such as MEG, PET, fMRI and ECoG, is important to cross-validate the results of an electrophysiological mapping. Co-registration of functional data is achieved by overlaying functional mapping results from various modalities onto structural MRI slices or MRI-reconstructed 3-D head models. Structural MRI data sets can have high spatial resolution to show the complex anatomical details of the human brain.

The general protocol for HR-EEG mapping uses magnetic resonance images to make 3-D realistic head models and an increased number of electrodes in the hope of improving the accuracy and display of electrophysiological data (Fletcher, Kussmaul, & Mangun, 1996). This method will be discussed in Chapter 3. Deblurring™, a scalp signal enhancement technique developed by Gevins and colleagues, will be applied on the scalp-recorded potentials to help map out the cortical area(s) responsible for the activity recorded (Gevins et al., 1999). Specific procedures for the SEP and VEP studies done will be explained fully in Chapter 4. Patient studies will be presented in Chapter 5.
This thesis attempts to determine:

1. whether additional information can be provided by HR-EEG mapping with Deblurring™ for studying electrical activity of the brain, and

2. whether HR-EEG data correlate with other functional brain mapping results, such as functional magnetic resonance imaging (fMRI) and electrocorticography (ECoG).
CHAPTER 3
THREE-DIMENSIONAL BRAIN MAPPING
BY HIGH RESOLUTION ELECTROENCEPHALOGRAPHY

HR-EEG maintains the benefits of using EEG for studying brain functions, namely high temporal resolution, low cost, non-invasiveness and adaptability to clinical settings. Moreover, HR-EEG expands the benefits of routine EEG by allowing the gathering of more data in the same amount of time as well as providing better resolution of the spatial characteristics of the brain's electrical activity. By sampling brain electrical activity at a density sufficient to accurately reflect those changes, EEG spatial resolution is improved. Gevins (1987 & 1990) concluded that the 3dB point of the spread function for conductance of potentials from the brain surface to the scalp averages about 2.5cm in adults. With 64 electrodes, the average inter-electrode distance is about 3.3cm. With 128 electrodes, the average inter-electrode distance is about 2.25cm (Gevins et al., 1994). This number of electrodes should adequately record scalp potentials to represent brain activity changes.

By using simulations, Fletcher et al. (1996) showed that adequate electrode density is more important for providing an accurate topographic map than selecting which interpolation method to use for generating topographic maps. Many research studies, both for clinical data (Morris, Lüders, Lesser, Dinner, & Klem, 1986) and EP data (Gevins et al., 1995 & 1996; Junghöfer, Elbert, Leiderer, Berg, & Rockstroh, 1997; Kristeva-Feige, Grimm, Huppertz, Otte, & Schreiber et al., 1997), have been done in the last 15 years with higher density of electrodes to improve EEG spatial resolution. Research studies that have been done in the last 5 years by two HR-EEG research labs (Babiloni, Babiloni, Carducci, Fattorini, & Anello et al., 1997; Gevins et al., 1994) have included the use of realistic head models to integrate full head HR-EEG topographic data with anatomical models based on magnetic resonance images.

The research data reported in this thesis have been processed by Manscan® (Beta 4.0 Version,
SAM Technology, San Francisco, CA, USA). Gevins and colleagues have contributed to neuroscience research by developing the HR-EEG analysis method adopted in the Manscan® program, and applying this technique in cognitive neuroscience research (Gevins, 1996 & 1998; Gevins et al., 1995 & 1996) and in somatosensory evoked potential research (Gevins et al., 1994). The role of the Department of Diagnostic Neurophysiology at BC’s Children’s Hospital, where the thesis research was conducted, is to perform pilot studies applying this HR-EEG technique to pre-surgical brain mapping.

The HR-EEG research study protocol can be divided into 7 parts:

- anatomical magnetic resonance image acquisition;
- recording electrode setup;
- EEG data acquisition;
- anatomical and EEG data alignment;
- off-line EEG data processing;
- topographic map generation;
- EEG data interpretation

### 3.1 Anatomical Magnetic Resonance Image Acquisition

Realistic head models generated from the patient’s own magnetic resonance (MR) images are used for HR-EEG mapping. Due to the variations in head size and geometry among people, coregistration of scalp-recorded brain electrical activity to a realistic anatomical model of a subject can improve accuracy of the integration of multimodal data and realistic localization of physiological events. This is especially important for pre-surgical mapping studies which require knowledge of the functional anatomy for a particular patient.

In order to generate MRI-derived realistic head models, anatomic MR images must be obtained. These images must be 2-D and are consecutive cross-sectional images of the brain in either the coronal,
sagittal, or axial plane. When the parameters, such as the spacing of the images and the arrangement of the slices are known, the MR images can be stacked together and the air-skin boundary re-constructed to generate a realistic head model. This is called surface rendering. It involves contouring the surface of the scalp and interpolating the space between image slices. If the MR images are high in density (i.e. small inter-slice distance, small pixel size, and high image spatial resolution), the difficulty of the rendering process diminishes as more data are available for interpolating the face tissue.

The use of a realistic head model is also a key improvement for estimating the cortical potentials from scalp-recorded EPs. The Deblurring™ section will describe how the anatomic MRIs are used to compute finite-element models of the boundaries of the inner skull, the outer skull, and the scalp. Source localization methods, such as DLM, can be improved by using a spherical model that fits best with the realistic head model. Moreover, showing computed dipole(s) in a MRI-slice or a reconstructed 3-D head improves interpretation of the functional anatomy.

Segmentation of the anatomic MRIs allows surface boundaries other than air and skin to be visualized. For example, anatomic MRIs of the head can be segmented to show the cortical surface of the brain before brain surgery. Cortical anatomy also provides important information for aligning anatomical, functional neuroimaging results, and intra-operative pictures (Appendix 1).

3.2 Recording Electrode Setup

A 84-channel or 128-channel cap system is used for collecting EEG or EP data (Electro-Cap International, Eaton, OH, USA). The advantage of using an electrode cap is that it reduces the time needed to apply many electrodes. Inter-electrode distances are fixed in the cap. The cap attaches and stretches to fit quite tightly on each subject’s head, so that the electrodes remain evenly on different subjects with a range of head sizes and geometry. Landmark positions (nasion, inion, and vertex) are used to orient the cap so that electrodes on the cap fall on their corresponding measured sites. The cap system
uses silver/silver-chloride (Ag/AgCl) electrodes carried in plastic holders. The conductive electrolyte used for maintaining contact between the recording electrodes and the scalp surface for an electrode cap system is Quik-Gel® (Neuroscan, Sterling, VA, USA), which breaks down scalp surface oil to lower the impedance of the recording electrodes.

Relative 3-D coordinates of all the recording electrodes and fiducial landmarks are computed from twenty-three straight-line measurements between electrodes and fiducial landmarks on the subject’s head by a pair of calipers (Mitutoyo MTI, Aurora, IL, USA) (Le, Lu, Pellouchoud, & Gevins, 1998). By using this method, a small number of direct measurements are needed to be made in order to compute the 3-D coordinates of all electrodes in the Extended 10-20 System of electrode positions. The average time for determining electrode positions by this method is less than 6 min (Le et al., 1998).

Electrodes are checked for their impedance before EEG data acquisition to ascertain optimal recording quality of each electrode. The total time for setting up electrodes for data acquisition can vary from 1-3 hours, depending on the number of electrodes used, the number of experimenters and, most importantly, the degree of difficulty of minimizing impedance.

3.3 Electroencephalographic Data Acquisition

EEG data are recorded by a Telefactor 128-channel Beehive System (West Conshohocken, PA, USA). EEG data are stored in analog form together with a video recording of the experiment on high-resolution video (S-VHS) tapes.

3.3.1 Recording System Settings

The EEG signals are amplified $10^4$ times. Data are initially referenced to electrode(s) plugged into the system reference(s) during data acquisition. During off-line data processing (Section 3.5), the digitized EEG data can then be re-formatted to another desired montage.
3.3.2 Recording Filter

Filtering is a signal processing method for limiting the frequency components contained in the electrical data. In most EEG machines, one particular built-in recording filter is set up for removing frequency components that may cause an aliasing problem. Aliasing is a problem where the sampled data produced by the analog-to-digital conversion process do not reflect the actual data due to the low sampling rate for the high frequencies in the EEG data (Figure 10). The Nyquist frequency is defined as half of the frequency of the sampling rate. EEG frequencies higher than the Nyquist frequency can create uncorrectable erroneous low-frequency components in the sampled data. Because of this, an anti-aliasing filter is usually built in the recording system as a low-pass filter set at or lower than the Nyquist frequency. Even if researchers are not interested in the frequencies above the Nyquist frequency in their data, the EEG data still need to be filtered before A/D conversion to prevent the aliasing problem, which can affect the whole frequency spectrum. The Telefactor Beehive System has a low-pass recording filter set at 70Hz.

3.3.3 Analog-to-Digital Conversion

The EEG data in analog form are converted to digital form in the Telefactor BeeKeeper System. The sampling rate is 200Hz and the A/D converter of the system transforms analog data to digitized form in 8-bit format. Then, the data files are imported into the Manscan® program for further data analysis and production of functional maps.
FIGURE 10  Aliasing Problem

ANALOG DATA

DIGITAL DATA (Sampled at $\frac{1}{2}$x A/D Conversion Rate of Figure 7)

Comparison with Figure 7:
Waveform is "flattened" and "straightened".
Features (e.g. peaks) are eliminated or reduced.

Consequences:
Digital data are distorted and different from actual (analog) data.
3.4 Alignment of Anatomical and Functional Data

The anatomical 3-D head model is reconstructed from the subject's MR slices, as described in Section 3.1. The 3-D coordinates of the recording electrodes (Section 3.2) carry information of the electrode positions over the subject's head. To accurately localize brain activity to the appropriate regions after analysis of the EEG data, the alignment of the 3-D head model and the electrode positions into a common coordinate system is required. This step maps the EEG electrode position matrix onto the subjects' head by aligning the coordinate system of electrode placement to match the coordinate system of the 3-D head model. This is achieved by using the three fiducial skull landmarks (the nasion (NAS) and the two preauricular points (PA1 and PA2)) as reference points. When electrodes are applied to a subject, their locations and the three fiducial skull landmark locations are measured. This gives information to calculate the coordinates of the recording electrodes for the EEG data. The same three fiducial skull landmarks are labelled in the realistic 3-D head model. The landmark coordinates from the electrode position measurement are first aligned and scaled to their positions in the head model. Then, the electrodes are mapped to their corresponding locations on the subject's head. Because a realistic 3-D head model and measured electrode positions are used, the functional mapping of HR-EEG activity is tailored to individual mapping studies.

3.5 Off-line EEG Data Processing

Because of the high number of channels and the vast amount of data obtained during a short HR-EEG recording session, the data are not interpreted directly in their raw form; rather, data are processed and summarized before interpretation and display.
3.5.1 Editing

Electrodes are checked for contamination by two means: first, by scanning the quality of the time-series data in each electrode; and second, by studying the frequency components of the data. The first method involves a quick reading of the EEG data for any dead channels, 60Hz contamination, electrode pops, or other artifacts. In the second method, data from each electrode are computed first into their corresponding power spectra by a discrete Fourier Transfer Algorithm (Section 3.5.4). Power spectra of electrodes which are contaminated with many isolated and discrete high-amplitude peaks unrelated to the expected rhythms and discrete events are judged to be “noisy” and rejected for further analysis. Expected high EEG frequency peaks are those corresponding to the stimulating frequency, its harmonics and the spontaneous rhythms, such as alpha. The remaining data are then subjected to analytic procedures for signal enhancement and extraction.

3.5.2 Post-hoc Filtering

Filtering is used on the recorded data to limit the frequency components. This is a useful technique for removing noise frequency, such as 60Hz from the electrical line interference, and for correcting DC offset problem. For example, muscle artifacts and low frequency noise can be removed from the raw data by setting the bandpass of the filter so that these artifacts lie outside the desired frequency band. However, if artifacts and noise occur near the frequency band(s) of interest, filtering is not appropriate because applying a filter near the signal band(s) can alter the signals by distorting their latency and amplitude (Regan, 1989).
3.5.3 Averaging

EPs are small and can be masked by noise, such they are not easily evident as single-trial responses in the EEG record. Enhancement techniques are needed to extract the signals from the background EEG data. It is then possible to localize brain areas responsible for generating the signals related to the stimuli. Averaging is a common technique to improve the S/N ratio of EP data.

Averaging involves aligning each stimulus and its responses for mathematical averaging in the time-domain. Evoked responses are expected to be time-locked to the stimuli. In contrast, noise, i.e. background EEG, is random and uncorrelated to the stimuli and can be either positive or negative in voltage. By simple addition, noise should cancel out. This way, the S/N ratio is improved (Figure 11). In theory, averaging N samples of a waveform improves the S/N ratio by a factor $\sqrt{N}$ (Regan, 1989, Appendix 1.1.1). Various kinds of EPs have different single-trial signal sizes. Different states of the subject change the background EEG waveform. Hence, different numbers of trials are required to generate satisfactory averaged EPs for various kinds of EPs. For SEP, usually 500-2000 trials are needed (Misulis, 1993). For VEP, usually 100-200 trials are needed (Misulis, 1993). The difference is due to the smaller amplitude of the evoked SEP responses than the VEP responses.

Caution is required when studying an averaged EP signal. It is possible that the averaged EP is quite different from single-trial EPs. EPs and EEG noise are not stable from trial to trial. For example, amplitude of the EP responses can be affected by arousal, selective attention and fatigue (e.g. Meador, Ray, Day, Ghelani, & Loring, 1998). Noise may not average to give a $\sqrt{N}$ improvement in S/N ratio if both EPs and EEG noise are varying from one trial to another by external factors unrelated to the stimuli.
FIGURE 11  Averaging

Selection of event trials

Alignment of timing of trials

Average voltage across trials
3.5.4 Signal Synthesis (Harmonic Frequency Extraction)

Signal synthesis is a stimulation frequency harmonic extraction technique. The assumption for the evoked potential extracted by this method is the same as for averaging: the EPs are time-locked to the stimuli. Hence, the periodic frequency of the responses in the recording is the same as the stimulus frequency. This method involves a different kind of “averaging” that is carried out in the frequency domain rather than in the time domain. This kind of averaging, called spectrum averaging, improves the S/N ratio of the signal frequency components represented in the data. It is used only for steady-state EPs and not transient EPs.

A block of steady-state evoked potential recording is a repetitive signal whose “harmonic components remain constant in amplitude and phase over many stimulus cycles” (Regan, 1989). A repetitive signal that “continues for an infinitely long time is equivalent to the sum of discrete, infinitely narrow frequency components, all of which are harmonically related and formed a Fourier series” (Regan, 1989). Although a steady-state EP recording is not infinite and the waveform is more complex and variable because of noise, it can be converted into the frequency domain as a block of data with high enough frequency resolution and signal power to distinguish the signal from noise. The signal frequency components are concentrated in narrow discrete frequency bands related to the stimulation frequency, and is thus a small fraction of the total EEG bandwidth. Biological noise, on the other hand, occurs throughout the EEG recording and is distributed over the whole power spectrum. If enough precaution has been taken to avoid time-locked artifacts in the recording, such as stimulus artifacts, this method allows a steady-state EP to be extracted from noise by the multiplication and integration procedure of Fourier. The responses are then expressed as a linear sum of discrete frequency components, which correspond to the stimulating frequency and its harmonics.
This frequency extraction method requires three separate operations: discrete Fourier transform, frequency extraction, and inverse Fourier transform (Figure 12) (Nakamura, Nishida, & Shibasaki, 1988). The whole block of raw data is transformed first into the frequency domain by discrete Fourier transform algorithm. Because the stimulation frequency is known and the steady-state EP power is narrow and concentrated in that frequency and its harmonics, the second step tries to improve the S/N ratio by removing the noise. The Fourier components carrying the signal frequency and its harmonics can be extracted by setting all other frequency bins to zero, such that the noise frequencies are eliminated in the power spectrum.

The last step is to transform the data back into the time domain by using the inverse Fourier transform. During the previous discrete Fourier transform step, one whole block of steady-state EP recording (in tens or hundreds of seconds) was transformed into a single power spectrum to achieve a high frequency resolution for identification of the proper extraction frequencies. After eliminating noise in the power spectrum and using only the signal frequency components lower than the Nyquist frequency for the inverse FFT step, the signal can be transformed to the time domain, with the periodic frequency of the evoked potential deduced from the stimulus frequency. The final result of signal synthesis is one period of the elicited signal. This signal is similar to the averaged evoked potential in the processed time series, although they can be out of phase if the original block of the steady-state EP recording does not start at the time of a stimulus. Even EPs recorded over the alpha frequency region, for example, can be extracted by this method if the S/N ratio is satisfactory because the EP power is confined to one or two bins, whereas the alpha power is spread over many bins in the region 8-11Hz.

Figure 13 shows the same somatosensory evoked response extracted by (A) averaging and (B) signal synthesis. The “averaged” EPs extracted by the two methods are similar in morphology if the steady-state recording is relatively clean, free from time-locked artifacts, and the stimulating frequency is regular.
FIGURE 12  Signal Synthesis

(SEP recording from a normal adult subject)
(13.71Hz, 0.2ms, 3.4mA electrical pulses applied at left index finger for 100s)

**EEG data in time domain**

(A CHANNEL NEAR RESPONSE AREA)

![EEG data near response area graph](image1.png)

(A CHANNEL AWAY FROM RESPONSE AREA)

![EEG data away from response area graph](image2.png)

**STEP 1: Discrete Fourier Transform (FFT)**

**Power spectral data (frequency domain)**

![Power spectral data graph](image3.png)

**STEP 2: Signal Frequency Extraction**

**Zeroing noise frequencies**

![Zeroing noise frequencies graph](image4.png)

**STEP 3: Inverse FFT**

**Signal synthesis data (averaged data in time domain)**

![Signal synthesis data graph](image5.png)

FIGURE 13  Extraction of Signals by (A) Averaging and (B) Signal Synthesis

(SEP recording from a normal adult subject)
(13.71Hz, 0.2ms, 3.4mA electrical pulses applied at left index finger for 100s)
3.5.5 Deblurring™

Spatial enhancement techniques have been developed to improve scalp EEG signals to reflect the cortical potentials better. Cortical potential modelling methods, such as Deblurring™, have been developed to compute the estimated cortical potentials from scalp-recorded raw EEG signals (Gevins et al., 1994 & 1999). Deblurring™ is the mathematical procedure for reducing the spatial blur distortion of the scalp-recorded brain potentials. This technique accounts for the transmission of the cortical potentials through the superficial cerebral cortical surface, using a finite element model of each subject’s scalp, skull and cortical surface. Current Source Density (CSD) or Laplacian derivation, improves the raw EEG signals by estimating the surface Laplacian of the electrical potential field and representing the hypothetical current flow entering and exiting the superficial cortical surface (Le, Menon, & Gevins, 1994). CSD and other spatial enhancement techniques help improve the scalp EEG signals for more accurate localization and mapping but they do not make use of a realistic finite element model.

In order to “deblur” scalp potentials, the resistivity of the electrical signals in the various tissue layers, and the thickness of these layers and skull must be taken into account. The resistivity of the cerebrospinal fluid is about 64 ohm-cm. The resistivity of a wet skull is about 20000 ohms-cm and that of the cortex is about 300 ohm-cm. The resistivity of the skull is roughly 80 times that of scalp or brain tissue (Nunez, 1981). The real skull contains several holes and areas of thinning. The human head is round but not exactly a sphere. These are factors that make correction of the scalp-recorded brain signals to show the cortical potential harder than it seems. To make the estimate better, the Finite Element Deblurring™ method, developed by Le and Gevins (1993) to enhance the scalp-recorded EEG and EP, uses a realistic 3-D model custom-made from each subject’s MRI. The resulting model is different from previous attempts to compute cortical potential from scalp-recorded potential. First, head models constructed from the subjects’ MRIs are used so that the model is geometrically correct (i.e. realistic). Second, the surfaces are modelled by finite elements, which take into account the regional differences
in scalp and skull thickness. Third, the computation is a forward "downward continuation" method. This means that the cortical surface potential is first estimated by a sparse solver to solve the Poisson's equation, which describes the potential distribution in the skull and scalp layers, with the boundary conditions defined in the head model. Then, using an iterative procedure, the cortical potential distribution that produces a forward solution of the computed scalp potential which best matches the actual measured scalp potential is accepted as the "deblurred" potential (Le & Gevins, 1993). Figure 14 shows the schematic diagram of the Deblurring™ method. For detailed data processing scheme, the readers are referred to the developers of this technique (Gevins et al., 1994).

The subject’s MRI data are required for defining the inner skull, the outer skull, and the outer scalp boundaries. A geometrically realistic model of the subject’s head is then made in the form of tetrahedral-shaped cells. This finite-element head model is called a Deblurring™ mesh. Textbook values are used for the scalp and the skull resistivity. Resistivity value of the scalp is defaulted to be 222 ohm-cm and the skull is 17760 ohm-cm (Nunez, 1981). With the thickness and resistivity of tissues determined, the computation can begin to search for the optimal "virtual" cortical potential.

The Deblurring™ method estimates cortical surface potential from non-invasive scalp recording without source localization. The inverse problem is not solved. The inverse problem refers to the problem of determining the electrical activity source which produces the recorded scalp potential distribution (Fender, 1987). This problem has no unique answer unless additional information and/or assumptions are available regarding the number of sources and the boundary of possible location(s) of the source(s) to allow choosing among possible candidate source models.
FIGURE 14 The Deblurring™ Method Scheme

RECORDED DATA

Anatomical MRI → Finite Element Model of the 3-D Head

Recorded Scalp EEG Data

DEBLURRING

Estimated Cortical Data → Compute forward solution of Poisson's equation using finite element method → Computed Scalp Data

Converged?

NO → Compute cortical data using optimization scheme

YES → STOP

(DEBLURRED DATA)

(Adapted from Le & Gevins: IEEE Trans Biomed Engin, 40: 517-528, 1993)
3.6 **Topographic Map Generation**

Topographic maps are means for visualizing the spatial distribution of the processed data efficiently (Wong, 1991). Topographic maps can be generated for both time-domain or frequency-domain data. 3-D topographic maps are produced by the Visualizer module of the Manscan® program. Maps for both scalp and deblurred EEG can be made and then compared to results from other functional studies by fMRI or ECoG. 3-D topographic maps of the average voltage at a particular time point or range, and the root-mean-square (RMS) values of the evoked responses, can be produced to show activated regions detected by the HR-EEG method.

3.7 **Data Interpretation**

3.7.1 **Scalp and Deblurred Electroencephalographic Result Comparison**

Comparison of scalp HR-EEG with routine clinical EEG can show how the higher density of electrodes changes the focus of the activity recorded. Comparison of the scalp HR-EEG data and the deblurred HR-EEG data can show if applying this analytic technique can further improve the mapping value of HR-EEG.

3.7.2 **Multimodal Functional Data Comparison**

The comparison of deblurred HR-EEG data with functional results collected by other neuroimaging techniques can show how well the EEG mapping results match with other functional mapping results. In order to compare results from various functional mapping studies, accurate registration of the functional data onto the subject’s realistic head model is crucial. For example, comparison between the cortical potential distribution recorded directly by ECoG and that computed by Deblurring™, and comparison between deblurred HR-EEG and fMRI result can be achieved when 3-D
functional maps co-registered on the same realistic head models are produced. The locations of the peak response cortical areas can be compared to see how congruent the various functional brain mapping results are. Alignment of the functional data is made possible by comparing surface landmarks, segmented cortical anatomy, and measured 3-D coordinates.

A series of studies on normal adult subjects and pediatric patients were performed to carry out the above comparisons as part of the pilot study of applying HR-EEG for pre-surgical functional mapping. Specific protocols and results for each study will be presented in Chapters 4 and 5. Overall conclusions for this series of studies will be discussed in Chapter 6.
CHAPTER 4
MAPPING OF THE PRIMARY VISUAL AND SOMATOSENSORY CORTICES IN ADULT VOLUNTEERS

4.1 Study A-1: Mapping of the Primary Visual Cortex Evoked by Hemifield Visual Stimulation

4.1.1 Background

4.1.1.a Visual Evoked Potentials (VEPs)

VEP is the evoked potential due to visual stimulation. There are many different types of visual stimuli that differ from each other by the visual field(s) stimulated, patterns, flicker rate, brightness, hue, and colour. Clinical VEP stimuli include flash, full-field pattern reversal and hemifield pattern reversal. VEP differs from most other evoked potentials by being a long-latency response (e.g. 100ms peak). The amplitude of the VEP is also relatively larger than other evoked potentials. Sometimes VEP can be visible in raw EEG data without averaging. If averaging is done, usually less than 250 trials are needed to obtain an averaged VEP that has satisfactory S/N ratio.

4.1.1.b Primary Visual Cortex

The occipital lobe contains the primary visual cortex along the banks of the calcarine sulcus. In humans, this cortex is located at the posterior pole of the cerebral hemisphere and lies almost exclusively on the medial surface. The visual field is the view seen by the two eyes without movement of the eyes or the head. The primary visual cortex contains an orderly map of the visual field. The upper fields are mapped below the calcarine fissure and the lower fields above it. Because the fovea receives a greater area representation than peripheral visual field, it has “higher resolution”. Each half of the visual field is represented in the contralateral hemisphere (Figure 15). The left hemifield projects to the nasal hemiretina of the left eye and the temporal hemiretina of the right eye. The right hemifield projects to
the nasal hemiretina of the right eye and the temporal hemiretina of the left eye. Nerve fibres of the nasal hemiretinas cross at the optic chiasm such that the left hemifield projects only to the right primary visual cortex and the right hemifield projects only to the left primary visual cortex.

FIGURE 15  The Visual Pathway
4.1.2 Objective and Significance

The objective of this study is to determine whether HR-EEG with Deblurring™ can localize regions in the visual cortex activated by right and left hemifield stimulation and how the results compare to fMRI mapping with the same stimuli. Previous studies and knowledge of the neural pathways suggested that the visual hemifield stimulation should activate the contralateral visual area (Regan, 1989). If the two mapping results converge, this can provide evidence for the accuracy of HR-EEG.

The significance of this study is that no previous attempts have been reported to utilize the HR-EEG method with Deblurring™ to study VEPs and compare localization with fMRI results. Results of the fMRI and HR-EEG data in this experiment have been published in abstract form (Dougherty, Au Young, Giaschi, Bjornson, & Wong, 1998). This thesis focuses on the collection and analysis of the HR-EEG results of this experiment, which was the author’s responsibility.

4.1.3 Study Procedure

4.1.3.a Subjects

Five adult volunteers were recruited to be subjects for this study. Subjects either have normal vision or use contact lenses to restore to normal vision. All subjects gave informed consent before both HR-EEG and fMRI experiments. The studies were conducted with the approval of the UBC and the BC’s Children’s Hospital research review committees. The subjects consisted of 3 males and 2 females with ages in the 20-30s range.

MR images were obtained at the Department of Radiology of the UBC Hospital for subjects 1-4 and of the BC’s Children’s Hospital for subject 5. Each volunteer underwent an anatomic MRI scan before acquisition of the fMRI data. The anatomic MRI data from the UBC Hospital were acquired transaxially with a GE Signa 1.5T scanner (Waukesha, WI, USA). The anatomic MR data for subjects 1 to 4 were T1-weighted with voxel size of 1mm x 1mm x 1.5mm (TR22ms/TE4.4ms/FOV 38.4cm/flip...
angle 30deg/thickness 1.5mm/matrix 256x256). The anatomic MR data from the BC's Children's Hospital were acquired sagittally with a Picker 1.5T scanner (Cleveland, OH, USA). The anatomic MR data for subject 5 was T1-weighted with voxel size of 1.2mm x 1.2mm x 1.2mm (TR22ms/TE4.4ms/FOV 38.4cm/flip angle 30deg/thickness 1.2mm/matrix 256x256).

4.1.3.b Visual Stimulation Parameters

The stimulus was a black and white half-dartboard contrast-reversing at 8 cycles per second (Figure 16). The visual hemifield stimulation was given to both eyes simultaneously, but to only one visual hemifield (left or right) at a time. The SVGA monitor was set to refresh at 67Hz and had a resolution of 640 x 480 pixels. The visual pattern was originally developed by Dougherty and Giaschi (1998) for fMRI study (Section 4.1.3.d).

For steady-state HR-EEG study, a 30-s trial for each visual hemifield stimulation in each subject was processed and analyzed. The monitor was placed at 80cm in front of the subject. The height of the monitor was adjusted so that the fixation spot at the centre of the dartboard was at eye level of each subject when his/her head was level.

For fMRI study, visual stimulation consisted of alternations of left and right visual hemifield stimulation blocks. Each block contained a 21-s trial stimulation and 6 blocks of stimulation was performed for each visual hemifield.
4.1.3.c HR-EEG Study Procedure

The study was carried out in a dimmed room. White noise was applied during the experiment to the subjects seated on an armchair. Because background EEG can be changed throughout the experiments by movement, attention, anxiety, noise, blinks, and visual movements, subjects were shown these effects on their EEG before the experiment started. Subjects were asked to minimize the above artifacts by being relaxed, but staying alert, throughout the experiment.

A 84-channel adult size-M Electro-Cap (Eaton, OH, USA) was used for the study. The reference electrodes were tied left and right mastoids. The ground was placed at the nasion. Because the data for the two visual hemifield stimulation were recorded in sequence, to avoid cross-contamination of data between the left and the right visual hemifield stimulation, only the middle 25-second block was included for analysis for each side of stimulation. There were over 400 trials for each block of visual hemifield data.
4.1.3.d fMRI Study Procedure

In each fMRI study session, the subject’s head was fixed in position during the experiment by straps and cushion when lying within the scanner. A mirror, anchored to the head coil of the MR machine at a 45°-angle, was positioned near the eyebrows to reflect visual stimuli from a rear projection screen mounted at the end of the MR bore near the subject’s feet. The visual pattern was presented through a window by a projector located outside the MRI room. The mirror and the visual pattern were adjusted so that the fixation point of the visual pattern lay in the middle of the subject’s visual field and that the whole hemifield pattern could be seen. The functional MR data were T2*-weighted with a resolution of 3 x 3 x 3 mm voxels (TR3500ms/TE40ms/FOV 38.4cm/flip angle 90deg/thickness 3mm/matrix 128x128).

4.1.3.e Data Analysis

The flow chart in Figure 17 illustrates the procedure for collecting and analyzing the HR-EEG and fMRI data for this experiment.

The anatomic MR images from each subject were used to make a realistic head-model as outlined in Section 3.1. Segmentation was done to extract the cortical surface boundary (Appendix 1) and tissue boundaries were identified from each subject’s MRI so that Deblurring™ could be performed on the scalp HR-EEG data.

Each subject had two separate sets of HR-EEG data: one for each visual hemifield stimulation. Each set was analyzed by the same method. The steady-state visual stimulation can cause electrophysiologic signals at twice the cycle reversal rate (i.e. the rate of turning the visual receptors on and off) and its harmonics. Power spectra were computed from the occipital channels and these exact signal frequencies were identified from the power spectra. Signal synthesis was used to extract the signals from noise and to produce the averaged VEP. The scalp VEP was then subjected to the Deblurring™ process for estimating the cortical potential. Both the scalp and deblurred results were
displayed in topographic maps for easy visualization of the activated regions. The root-mean-square (RMS) value of the response in each channel and the interpolated values for inter-electrode areas were mapped to the 3-D head models. The more activated a region was, the higher the RMS value.

fMRI data were analyzed by the SPM96 software (Friston, Holmes, Worsley, & Poline et al., 1995). The fMRI data analysis used all 6 stimulation blocks to generate an activation map for each visual hemifield in each subject. The spatial parametric mapping analysis is voxel-based and uses the General Linear Model “to describe the variability in the data in terms of experimental and confounding effects, and residual variability at the voxel level with univariate statistics” (Friston et al., 1995). The resulting image has voxel values which represent the statistical results. The more activated a region was, the more significant the statistical results.
FIGURE 17  Procedural Flow Chart for Visual Hemifield Study (Study A-1)

Subjects (n=5)

Anatomic Magnetic Resonance Imaging (MRI)

High Resolution Electroencephalography (HR-EEG) (Steady State Analysis)

Scalp Electrode Cap Application (84 Electrodes)

Measurement of Electrode Positions

Brain Segmentation

Hemifield Visual Stimulation

Scalp EEG 3D RMS Map

Harmonic Frequency Extraction

Left Hemifield Epochs

Statistical Parametric Mapping

Deblurring

Deblurred EEG 3D RMS Map

Skull Thickness Determination

Right Hemifield Epochs

fMRI Activation Map

Left Hemifield Epochs

Functional Magnetic Resonance Imaging (fMRI) (SPM96 Analysis)
4.1.4 Result

The stimulation frequency was 16.675Hz and 1 harmonic could be identified from the power spectra (Figure 18). Figure 19 shows the scalp 3-D topographic map (left), the deblurred 3-D topographic RMS map (centre), and the fMRI activation map (right) of each subject. The subjects' head renderings were orientated such that each subject “looked into the page”, and the back of the heads are visible for readers to access activation in the occipital lobes. The topographic maps used a colour scale that represented the region with the maximum RMS value, thus the most activated, red; the 50% value, white; and zero, blue. The fMRI maps showed the most activated cortical region as yellow. The activated regions detected by fMRI were buried in the cortices and were made visible by simulating the angled cut of the deblurred maps and removing oblique MR slices superior to the activated region. Both HR-EEG and fMRI data of each subject were registered on the same realistic 3-D head model constructed from the subject’s anatomic MRI set.

**FIGURE 18** Visual Stimulation Frequency and Harmonics

**POWER SPECTRA OF OCCIPITAL ELECTRODES**

[Graph showing power spectra with peaks at 16.675Hz, labeled as 16.675Hz (2x reversal rate)]

Bin size: 0.025Hz
FIGURE 19  Results of Visual Hemifield Study (Study A-1)

Each triplet represents a subject’s mapping results of either the left or the right visual hemifield stimulation. The left map shows the scalp RMS voltage (μV) of the visual evoked response. The centre map shows the deblurred RMS voltage (μV) of the visual evoked response. The right map shows the fMRI activation in a z-score scale. In the fMRI maps, the voxels were defined to be activated and coloured when they were found to be significantly brighter with one hemifield stimulation than the other (p<0.01, corrected). The colour scale was maximized individually (0-max) for each map.
FIGURE 19 (continued)  Results of Visual Hemifield Study (Study A-1)

Subject 4

Subject 5

KEYS:
- Scalp and Deblurred EEG
- RMS voltage (μV)
- fMRI
- z-score

Direction of Cuts for Exposing Cortical Surface and Direction of Complementary fMRI Slices
The scalp topographic maps showed visual area activation in all subjects. Left hemifield stimulation activated contralateral (right) visual cortex in all subjects. Subjects 1 and 5 showed quite exclusive activation in the contralateral visual cortex. However, activation was found to be more midline in subjects 2 and 4, and was hard to judge to involve contralateral, ipsilateral, or both visual cortices from the scalp topographic maps. Subject 3's activation spread to the ipsilateral (left) hemisphere and was more extensive in the ipsilateral than contralateral hemisphere. Right hemifield stimulation activated contralateral (left) visual cortex exclusively in subjects 1 and 4. In subjects 2, 3 and 5, the activation occurred at the midline in the inter-hemispheric fissure. Subject 3's activation also spread to the ipsilateral (right) visual cortex.

The deblurred topographic maps localized activation to the occipital poles in all subjects. In subjects 1 and 5, the deblurred maps for left hemifield stimulation localized the activation to the contralateral (right) occipital poles exclusively. The deblurred maps for subjects 2, 3, and 4 showed more midline occipital activation for left hemifield stimulation. The deblurred map for subject 4 showed maximum activation occurring at the contralateral (right) occipital pole, but spreading to the ipsilateral (left) parietal lobe for left hemifield stimulation. Deblurred maps for right hemifield stimulation in subjects 1, 2, and 5 showed midline occipital activation. In subject 4, the maximum activation occurred at the midline, but the activation incluse the contralateral (left) occipital area. In subject 3, maximum activation could be found quite exclusively in the ipsilateral (right) occipital lobe.

The fMRI maps showed contralateral occipital lobe activation for both hemifield stimulation in all subjects. Subject 4's activation spread to areas that were more anterior and superior (near the parietal-occipital boundary) than other subjects for both left and right hemifield stimulation.
4.1.5 Discussion

In clinical EEG, the precise locations of the electrodes are not available. The scalp HR-EEG data registered on each subject's 3-D head model allowed the actual location of the activation to be seen, rather than in reference to a certain electrode. Deblurred maps showed the activated cortical region better than scalp maps by registering the actual neuroanatomic structures with the functional data. Visualization of the activation pattern on the cortical surface further improved the ability to infer the location of the maximum activity. However, because of the locations of the occipital poles, the edges of the finite element tissue boundary models fell over the occipital cortical areas and no electrodes could be easily placed inferior to the occipital area, making it hard to clearly see the activation area. It was not possible to make a more stable and better finite element tissue boundary model because the neck muscle made the scalp and skull thickness increase suddenly near this area. This complication of anatomy made it hard to model the skull and scalp thickness near the base of the occipital lobe.

Some of the HR-EEG data showed ipsilateral activation in the visual cortex which was at odds with the expected visual pathway. The hemifield response occurred in the medial surface of the occipital pole near the calcarine sulcus. Barrett, Blumhardt, Halliday, Halliday, & Kriss (1976) and Blumhardt & Halliday (1979) explained that a visual evoked potential could be recorded in the ipsilateral rather than the expected contralateral hemisphere due to volume conduction and dipole orientation. Although the source of the activation occurs at the contralateral hemisphere, the topographic maps can show maximum activation at locations contralateral to the source, i.e. ipsilateral to the hemifield stimulation. This is called the “paradoxical lateralization” phenomenon. This may be the cause of the discrepancy between the scalp and deblurred topographic patterns and the fMRI activated regions in this study. Proper control of the stimulated visual field was adopted during the recording and the chances of cross-contamination of data between the two hemifield stimulation were minimized. Therefore, chances of procedural error had been ruled out as much as possible but still ipsilateral activation was recorded.
In an attempt to show that the "paradoxical lateralization" phenomenon could explain the results of this study, the dipole for subject 3's data for the right visual hemifield stimulation was computed with a 3-layer spherical model best fitted to the realistic head model (Fender, 1987). The resulted dipole was located in the occipital lobe contralateral (left) to the visual hemifield as expected (Figure 20). The dipole pointed towards the ipsilateral (right) occipital lobe, which could explain why the scalp topographic maps showed maximum activation there instead of the contralateral (left) hemisphere (Goodness of fit>85%).

The location of the source suggested that if ECoG could be done on subject 3, the real cortical VEP would be recorded from the medial contralateral (left) occipital surface. This is because cortical potential is not affected by volume conduction through the intracranial space and the recorded electrodes can be placed directly on the cortical surface, even possible for the medial surface. However, the deblurred response was constructed from the scalp-recorded response and no scalp electrodes could be placed normal to the medial surface. The midline electrodes on the scalp over the occipital lobes could pick up activity from both hemispheres. The Deblurring™ process attempted to correct the blur distortion of the scalp signals, but medial cerebral activity was difficult to be spatially enhanced because the Deblurring™ meshes did not model the inter-hemispheric fissure, which had two opposing surfaces. Electrical activity surface distribution caused by medial and/or deep sources after the Deblurring™ process can continue to be difficult for direct inference of source locations. Source localization techniques, such as DLM, are needed to solve the inverse problem.
High RMS voltage, indicating high EEG activity, was recorded in the right visual cortex during right hemifield stimulation.

Dipole localization demonstrated a probable source in the contralateral visual cortex, directed toward the surface of the occipital pole ipsilateral to the right hemifield stimulation. fMRI also showed activation in the contralateral visual cortex.
4.2 **Study A-2: Mapping of the Primary Somatosensory Cortex by Electrical Stimulation**

This study involves mapping the finger area of the sensory cortex in one adult subject. The hand area in the sensory homunculus suggests that the location of activation is far away from the medial surface, which allows the study of the Deblurring™ process without problems related to making good head models and to the paradoxical lateralization phenomenon as observed in the visual hemifield study.

4.2.1 **Background**

4.2.1.a **Somatosensory Evoked Potentials (SEPs)**

SEP is the evoked potential produced by the stimulation of the peripheral sensory nerves. The peripheral nerves commonly stimulated for clinical testing include the median, ulnar, peroneal, and posterior tibial nerves. During clinical SEP testing, a brief electrical pulse is delivered to the distal portion of the nerve. The typical SEP waveform for median nerve electrical stimulation is shown in Figure 21 (Desmedt, Nguyen, & Bourguet, 1987; Goff, Matsumiya, Allison, & Goff, 1977). Usually, about 1000 sweeps are needed to get a clean averaged SEP waveform.

**FIGURE 21** The “Typical” SEP for Median Nerve Electrical Stimulation

![Typical SEP waveform](image)
Cortical activation is believed to be responsible for the component peaks occurring 20ms or later after median nerve stimulation (Desmedt & Cheron, 1982; Yamada, Kayamori, Kimura, & Beck, 1984). The N20/P20 SEP component has been shown to be easily modelled by a single equivalent current dipole model, which makes it an appropriate candidate for pre-surgical mapping and investigation of plasticity of the sensory cortex (Kristeva-Feige et al., 1997). Because the electrical pulse can stimulate any nerve fibres in a mixed nerve, motor nerves can be stimulated as well when the stimulating current is high. The clinical SEP stimulating frequency is usually set at 4-7 Hz.

Mechanical somatosensory stimulation includes vibrations and air-puffs. A mechanical stimulus is considered to be more “natural” and more comfortable than an electrical stimulus. Specific mechanical stimulation of the finger, for example, may be able to provide information about a particular group of receptors and their nerve pathways (Pratt, Starr, Amile, & Politoske, 1979). The cortical potential evoked by electrical stimulation of the digital nerves and mechanical stimulation of the fingernails were shown to be similar, although the mechanical SEP were lower in amplitude and contained fewer components than the electrical SEP along the somatosensory pathway (Pratt, Politoske, & Starr, 1980).

4.2.1.b Primary Somatosensory Cortex

Electrical pulses directly stimulate the sensory nerves bypassing the sensory receptors. There are different types of sensory receptors, namely Meissner’s corpuscles, Pacinian’s corpuscles, Merkel’s receptors, and Ruffini’s corpuscles. A gentle electrical shock, mechanical vibrations, or air-puffs activate the tactile sensory pathway.

The primary sensory neurons start from the receptors in the periphery and travel to the dorsal roots of the vertebral column. Digital nerves and median nerves are examples of primary sensory nerve fibres. Nerve impulses travel upwards in the dorsal roots and synapse with the second order neurons at the medulla then cross the midline. The secondary order neurons send the sensory response from the
brain stem to the thalamus via the medial lemiscus tract. The thalamic nucleus responsible for fine touch is the ventroposterolateral (VPL) nucleus. The sensory response is then sent to the post-central cortex, which is the primary somatosensory cortex.

The primary somatosensory cortex is located at the posterior bank of the central sulcus (Brodmann’s areas 3a and 3b) and on the surface of the post-central gyrus (Brodmann’s area 2) (Allison, McCarthy, Wood, Parcey, & Spenar et al., 1988; Fox, Burton, & Raichle, 1987). The primary somatosensory cortex is known to be somatotopically organized (Penfield & Rasmussen, 1950). Two classical methods to determine somatotopy in post-central somatosensory cortex are direct cortical surface recordings of somatosensory evoked potentials (i.e. Goldring’s method), and observations or subject’s reports of sensations elicited by electrical stimulation applied on the post-central cortical surface (i.e. Penfield’s method). The sensory homunculus was mapped by Penfield and colleagues through direct stimulation of the post-central cortical surface (Penfield & Boldrey, 1937; Penfield & Jasper, 1954). Penfield and Boldrey (1937) found that the thumb area is more lateralized than the index area, index more lateralized than the middle, and so on. Sutherling, Levesque, and Baumgartner (1992) showed that the finger cortical representations were non-overlapping and the size order of the mapped areas by ECoG from the largest to the smallest was the thumb, index, middle, little, and ring finger.

Other cortical areas involved with somatosensory information processing include the lateral (Sylvian) sulcus region, which is termed the second somatosensory area (SII) (Kelly & Folger, 1999; Lee & Whitsel, 1992; Simoes & Hari, 1999). Various sensory association areas are responsible for integrating somatosensory information with other sensory systems, such as with the visual system (Brodmann’s areas 5 and 7) and with the motor system (the pre-motor cortex (PMC) and the sensorimotor association area (SMA)). These secondary areas may receive somatosensory information, not from the primary somatosensory area, but directly from the thalamus (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997).
4.2.2 Objective and Significance

This part of the study attempts to map out the primary somatosensory area by the HR-EEG with Deblurring™ method. The purpose of this study was to investigate if the precision of HR-EEG mapping was improved by Deblurring™. If the details of routine clinical EEG maps differed significantly with the HR-EEG maps, the extra cost, time, and expertise for analyzing data from using more electrodes for clinical EEG studies could be justified. If Deblurring™ improves EEG mapping by being more consistent and precise, this is evidence for the internal validity of this technique.

Due to the fact that electrical stimulation was used, an alternate method of somatosensory stimulation would be needed for a corresponding fMRI study, which has not been done at this time. Moving electrical currents can influence MR images unless properly shielded from the RF frequency used in acquiring MR images. Because other neuroimaging results are not available, the accuracy or the external validity of the mapping results was not studied. The SEP mapping in the patient studies in Chapter 4 will provide some data for that research question.

Clinical SEP testing is a tool for the diagnosis of spinal cord diseases, e.g. multiple sclerosis. It is used intra-operatively for monitoring surgical procedures to ensure the peripheral nerves are intact. For example, in surgery for correcting spinal scoliosis, SEP testing is used to monitor the sensory nerves to ensure they are not severed during the spine correction. For excisional surgery in patients with a brain tumour or epileptic activity in the sensory cortex, SEP testing is used to map out the sensory areas so that cortical regions responsible for sensory function can be left as intact as possible, while allowing the tumour or the epileptic zone to be removed.
4.2.3 Study Procedure

4.2.3.a Subjects

One adult volunteer, 25 years of age, was recruited to be the subject for this study. The subject was free of neurological disease and gave informed consent before the study. The study was conducted with the approval of the UBC and the BC's Children's Hospital research review committees. Two separate HR-EEG study sessions (2 months apart) were conducted to collect SEP data from 10 trials of left index finger stimulation (4 trials in the first and 6 trials in the second session) and from 9 trials of right index finger stimulation (3 trials in the first and 6 trials in the second session). The subject cleaned his hair before coming in to participate in the experiment and the impedance of all recording channels was 10kΩ or less.

The anatomic MR data consisted of T1-weighted images with voxel size of 1.5mm x 1.5mm x 1.5mm (TR22ms/TE4.4ms/FOV 38.4cm/flip angle 30deg/thickness 1.5mm/matrix 256x256). They were acquired at the BC's Children's Hospital sagittally with a Picker 1.5T scanner (Cleveland, OH, USA). The structural MR images were obtained prior to, and independent of, the HR-EEG recording sessions.

4.2.3.b Somatosensory Stimulation Parameters

Electrical impulses were applied to the index fingers by ring electrodes. Two sets of ring electrodes were used for attachment to both index fingers around the middle and proximal phalanges before the experiment started. The cathode electrode was proximal to the anode electrode by about 2cm. Electrode gel was used to help conduction of the electrical current. The sensory current intensity threshold was determined prior to actual recording. This was the lowest current intensity at which the subject could detect the electrical stimuli and was found to be 1.6mA for this subject. The stimulating current intensity was set to be 6mA, which was about 3.5 times the sensory threshold. The stimuli were lower than the motor threshold, and no involuntary movement, such as finger twitch, was visible during
stimulation. The stimuli were generated and delivered by the Neuropack 4 Mini EP machine (Nihon Kohden, Japan). The electrical impulses had a pulse duration of 0.2ms and were delivered at a rate of 13.7Hz. The stimulation time points were labelled by a marker generator in an extra EEG channel by 15ms-long pulses. A similar stimulating frequency had been utilized before (Gevins et al., 1994) in a previous HR-EEG with Deblurring™ study. The order of left or right side stimulation was random and the subject was blind to the order. Each trial lasted 100s in the first study session and 150s in the second study session.

4.2.3. c HR-EEG Study Procedure

The study was carried out in a dimmed room. The subject was seated on an armchair. Because background EEG can be changed throughout the experiments by movement, attention, tension, noise, blinks and visual movements, the subject was shown these effects on his EEG before the experiment started. The subject was asked to minimize the EEG artifacts by being relaxed but staying alert, eyes open and fixated to a point about 1m away at eye level throughout the experiment. His hands were rested comfortably on a hard surface at lap level with the palms down during the index finger stimulation. The subject was asked to keep his fingers separated and hands apart during the experiment to prevent stimulation at sites other than the index finger.

EEG was recorded by the Telefactor Beehive System (West Conshohocken, PA, USA) with a 84-channel adult size-M Electro-Cap. The reference electrodes were tied left and right mastoids. The ground was placed at the nasion. The recording system had a bandwidth of 0.1-70Hz.

The flow chart in Figure 22 summarizes the procedure for collecting and analyzing the HR-EEG for this study.
FIGURE 22 Procedural Flow Chart for SEP Study (Study A-2)

Test Subject / Patient

SEP Experiment (Functional Study)

Electrode Cap Application & 3D Electrode Position Measurement (3.2)

SEP Recording (3.3)

Data Editing & Signal Extraction (3.5.1-3.5.4)

HR-EEG Scalp Data

Anatomical MR Scan (3.1)

Alignment of Anatomical and Functional Data (3.4)

Construction of 3-D Realistic Head Model

Segmentation of Cortical Surface

Construction of Deblurring Meshes

Deblurring Process (3.5.5)

Routine Scalp Data

HR-EEG Deblurred Data
4.2.3.d Data Analysis

Data for each trial were digitized, edited, and filtered with a post-hoc filter of 1-55Hz to correct DC-offset and muscle artifacts. Signal synthesis was used to extract the signal from noise and to average the responses within each trial. The HR-EEG data were processed by Deblurring™ to make the deblurred data set. EEG recording from the routine EEG electrodes, namely, FP2, FP1, F3, F4, F7, F8, FZ, C3, C4, CZ, T7, T8, P3, P4, P7, P8, PZ, O1, and O2 were also used to compute a down-sampled data set.

The topographic map for each trial was made to show the response amplitude (in microvolts) in each channel and the interpolated voltages for inter-electrode areas at the time the highest positive evoked peak was recorded by an electrode in the contralateral central region. Positive rather than negative peak was used because the amplitude was larger with a better S/N ratio. Candidates for peak channels in the central region were C1, C3, C155, CP1, CP3, CP155, P1, and P3 for the left sensory cortex and C2, C4, C255, CP2, CP4, CP255, P2, and P4 for the right sensory cortex. Figure 23 shows how a peak channel was selected from a trial. The SEP peak full width at 80% maximum height was made visible by thresholding the colour scale in each map such that the “response area”, defined as having a voltage from 80% to the maximum recorded potential in this study, was coloured red. This was done for all the scalp and the deblurred HR-EEG maps for subsequent comparison between them. Each scalp or deblurred HR-EEG map was orientated such that the responding primary post-central cortex, defined as the regions of interest bounded by electrodes C1-CP1-C3-CP3 at the left and electrodes C2-CP2-C4-CP4 at the right, lay flat on the screen. By using the NIH Image software (W. Rasband, Bethesda, MD, USA), the magnitude of the flat 2-D response area was computed.
FIGURE 23 Selection of Peak Channels for SEP Study (Study A-2)

Deblurred data for a trial of left index finger stimulation

Highest positive peak belongs to C2, with amplitude of 6.31 µV at a latency of 0.021 s post-stimulus.
The size of the response area for each trial was used to indicate the precision of the mapping results. The more localized and smaller the response area was, the more precise the result was. For fair comparison between the scalp HR-EEG data and the deblurred HR-EEG data, adjustment was needed on the scalp data to account for the difference between the radii of the scalp and of the cortex from the centre of the skull. The scalp areas were corrected by these scaling factors before comparing to the deblurred data. In essence, the estimated “backward projected” areas from the scalp to the cortical surface were used to compare with the deblurred areas.

A scaling factor for converting the scalp area enclosed by electrodes C1, CP1, C3, and CP3 to the cortical surface area enclosed by the projected locations of the same electrodes was computed for the left primary sensory cortex activation maps. Ten measurements of the C1-CP1-C3-CP3 areas in the scalp maps and ten measurements of the projected areas in the deblurred maps were made. The scaling factor was then computed from the averaged areas of the two sets of measurements. A scaling factor for the right sensory cortex activation maps was computed similarly for the C2-CP2-C4-CP4 areas. The scaling factor for the left sensory cortex, which was used for adjusting the right index finger stimulation data, was 1/1.52 or 0.658. The scaling factor for the right sensory cortex, which was used for adjusting the left index finger stimulation, was 1/1.58 or 0.633. The two scaling factors were different because they were computed independently. They were affected by the electrode positions and the orientation of the 3-D head to make the regions of interest lay flat on the screen. This means that the regions of interest for the two hemispheres were not exact mirror images.

The scalp or the deblurred response areas of all trials were measured the same way. The deblurred areas and the “backward projected” areas from the scalp to the cortical surface were statistically tested for significant difference by t-test.
4.2.4 Result

By looking at the power spectrum of the marker channel, the exact stimulating frequency was computed to be 13.715Hz. Two harmonics were extracted by signal synthesis to compute the averaged results.

Figure 24 shows the routine scalp EEG and the scalp HR-EEG maps for one trial of the right index finger stimulation. Both maps showed activation in the expected left post-central region. However, the full-width 80% maximum area in the HR-EEG group was smaller than the EEG group. The EEG map was computed from a down-sampled subset of the scalp HR-EEG data. This shows how the higher spatial resolution of HR-EEG improved the identification of the somatosensory response area.

The scalp HR-EEG data for the left index finger stimulation showed maximum activation in C2 in 6 out of 10 trials (Table A-1). In only 2 trials, the peak electrode was the routine EEG electrode, C4. After Deblurring™, the peak electrode was identified to be C2 in 9 trials (Table A-3). For the right index finger stimulation, the peak scalp electrode was C1 in 3 out of 9 trials (Table A-2). In only 1 trial, the peak electrode was the routine EEG electrode, C3. After Deblurring™, C1 was the peak electrode in 7 trials (Table A-4). The results showed that a dense recording electrode array in the region of interest can better sample the evoked potentials; and after Deblurring™, the peak electrode was more consistent across trials in both the left and right index finger stimulation.
Thresholding of the colour scale was done individually in each map to show only the mapped area with an averaged evoked response at 80%+ voltage (µV) of the highest averaged positive evoked peak amplitude recorded in the contralateral post-central region in each trial. Each map represents scalp voltage activity at the time of the apex of the selected peak component of a right index finger stimulation trial of this subject.

**A**

**Routine EEG**

Routine EEG electrodes (19 in total):

FP2, FP1, F3, F4, F7, F8, FZ, C3, C4, CZ, T7, T8, P3, P4, P7, P8, PZ, O1, O2

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**B**

**HR-EEG**

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Figure 25 shows the scalp and the deblurred HR-EEG maps of all trials. The left index finger stimulation had an averaged adjusted full-width 80% maximum scalp area of 15.64cm$^2$ (S.D.=6.68cm$^2$) and an averaged deblurred area of 10.41cm$^2$ (S.D.=3.79cm$^2$). By a 2-tailed heteroscedastic t-test comparison, the peak spread areas between the two groups were shown to differ significantly (p<0.05).

A similar analysis was performed for the right index finger stimulation. However, the t-test result was not significant. The averaged adjusted full-width 80% maximum scalp area was 17.53cm$^2$ (S.D.=5.03cm$^2$) and the averaged deblurred area was 12.27cm$^2$ (S.D.=8.02cm$^2$). The insignificant result was probably due to the large standard deviation for the averaged deblurred area.

Deblurring® produced a smaller and less variable SEP spread area than the direct projected spread area for the left index finger stimulation. There was a 33.5% reduction of the averaged full-width 80% maximum area for the left index finger stimulation.
Thresholding of the colour scale was done individually in each map to show only the mapped area with an averaged evoked response at 80%+ voltage (µV) of the highest averaged positive evoked peak amplitude recorded in the contralateral post-central region in each trial. Each map represents scalp or deblurred voltage activity at the time of the apex of the selected peak component of a left index finger stimulation trial of this subject.
Thresholding of the colour scale was done individually in each map to show only the mapped area with an averaged evoked response at 80%+ voltage (μV) of the highest averaged positive evoked peak amplitude recorded in the contralateral post-central region in each trial. Each map represents scalp or deblurred voltage activity at the time of the apex of the selected peak component of a right index finger stimulation trial of this subject.
4.2.5 Discussion

This SEP study differed from clinical SEP studies which use a transient stimulation. In clinical SEPs, only a few electrodes are usually used. Usually, C3' and C4' (2cm distal to the measured C3 and C4 locations) are used for recording and nerve conduction may be monitored at the same time. The present recording setup was different from the clinical SEP studies to allow recording of many channels simultaneously. In pre-surgical mapping, whole head recording allows studies of both EEG (for spontaneous activity and seizure), and EPs (for various modes of functional studies, such as sensory, motor, and visual) with the same electrode positions. Thirdly, clinical SEP studies stimulate the median nerve directly, and not the digital nerves.

The recorded SEP components were less discrete and more smoothened than typical averaged SEPs; thus harder to identify from the averaged response. This reduction in response amplitude was not due to a low stimulation current intensity, but rather a physiological difference of the SEPs elicited by steady-state versus transient electrical pulses (Iramina, Kamei, Uchida, Kato, & Ugurbil, 1999; Synder, 1992).

Because digital nerves were stimulated, the SEP responses were small in amplitude even after averaging more than 1000 samples in each trials. Since whole head activity was measured and the SEP was small, the noise activity recorded by electrodes outside the sensory cortex could affect the S/N ratio in the topographic map even though the noise activity was not related to the stimuli. To reduce muscle artifacts, a post-hoc filter with a low-pass setting of 55Hz was applied to the data before signal synthesis. Most SEP studies have a upper recording filter setting of 3000Hz to record short-latency SEP components (Desmedt & Cheron, 1982; Misulis, 1993). Because the recording bandpass was up to 70Hz only, this post-hoc filtering step should have limited effect on the averaged SEP. The cortical response by the steady-state SEP stimulation still should contain the cortical components at 20ms or more after the stimulus. Peak amplitude, however, may be diminished, distorted and latency prolonged by the available
recording bandpass (Synder, 1992). This was evident in the results as the averaged SEP in some trials was quite small with a low S/N ratio.

The expected activation is focal and located at the lateral contralateral post-central region. A more medial, anterior and wider spread activation is seen in the contralateral pre-central region. The P22 and N30 SEP components have more anterior and medial scalp distributions than the N20 component (Desmedt & Cheron, 1982). It is possible that the N20 component might have less significance in the SEP responses in some trials than the P22 and N30 components, such that a more anterior activation was visible and picked instead. Since a steady-state stimulation protocol was employed and a narrow recording filter was available, EP components were not easily separable in the averaged response tracings. The N20 and the N30 components were not easily distinguished from each other in the averaged responses. Similarly, P30 and later positive P50 component, which were recorded post-centrally, and P22 which was recorded pre-centrally, were difficult to distinguish from each other.

The contribution of other cortical regions, such as the association areas and SII, also could affect the resulted topography. It is generally accepted that multiple brain areas contribute to the generation of the SEPs, but the source of N20 was located post-centrally (Cakmur, Towle, Mullan, Suarez, & Spire, 1997). A follow-up study could be done with a recording by a wider bandwidth and a transient stimulation protocol at the median nerve. These adjustments can produce more stable scalp SEP with high S/N ratio because the SEP has been shown to be smaller for high than low stimulation frequency (Snyder, 1992). Moreover, one specific component (e.g. N20) could be picked for analysis.

Attention, relaxation and alertness levels of the subjects seem to play a factor in the results of the experiment as the amplitude of the averaged signals reduced in later trials. Longer trial length for trials in the second study session did not produce a more consistent signal as hoped because the subject might have more difficulties maintaining his attention and alertness throughout the trial.
Even with a less than ideal SEP response, Deblurring™ was still shown to improve the mapping value of the SEP by the HR-EEG procedure by providing a more focal and consistent response area than the averaged scalp-projected area in the left index finger stimulation. For the right side, the t-test was insignificant. The standard deviation for the deblurred response area for the right index finger stimulation was relatively large, and the deblurred areas in two trials were larger than the scalp areas, which went against the trend for all the other measurements. This could be due to the low S/N ratio of the selected components, which subsequently affected the Deblurring™ process. However, these two particular trials did not have the smallest recorded peak amplitude among all trials in both sides. The response areas for these two trials were relatively large, but also not the biggest ones among all the measurements. The method for determining the scaling factors played some roles in introducing some imprecision in the computation. It was an unbiased way to compute the response areas and could not explain why only two trials in the right stimulation went against the trend for Deblurring™ to provide a more consistent and focal response area. This observation deserves further investigations.
CHAPTER 5
MAPPING THE PRIMARY SOMATOSENSORY CORTEX AND EPILEPTOGENIC ZONE IN PEDIATRIC BRAIN SURGERY PATIENTS

This chapter discusses the application of HR-EEG for pre-surgical mapping in two patients who required brain resection. Epilepsy surgery seeks to remove the brain region(s) that cause(s) seizure and will be the focus of this chapter. Functional brain mapping (for both normal brain activity such as SEP and motor potential, and abnormal brain activity such as seizure activity) plays an important role of accessing brain regions responsible for specific functions of the surgical candidates before the excision of brain tissues. In these two studies, 128 channels were used for collecting HR-EEG data.

5.1 Role of Electroencephalography in Epilepsy Surgery Planning

Epilepsy affects about 1% of the general population; many of them are children. It is mostly prevalent in children under 10 years of age (80 per100000) and in people over 60 years (82:100000). Epilepsy is a condition characterized by a tendency to manifest recurrent seizures (2, 3 or more) not attributable to an immediate known cause (Duncan, Shorvon, & Fish, 1995). Epilepsy is best viewed not as a single condition, but rather as a symptom of neurological disorder. The clinical manifestations depend upon the cause of the epilepsy, the anatomical location within the brain of the epileptic focus, the pattern of spread of epileptic discharges through the brain, and also upon the age and the level of cerebral maturity of the patient. EEG is the standard clinical diagnostic test for epilepsy. Using HR-EEG may provide more detailed information of brain activity associated with seizures in patients and may allow for better localization of brain areas from which the seizures originated. This is extremely important for patients who seizures need to be controlled by surgical methods (Binni & Stefan, 1999). It is hoped that by using HR-EEG with Deblurring™, non-invasive pre-surgical mapping can be done to study the cortical regions responsible for generating the seizures and the cortical regions responsible for
somatosensory, motor, and speech functions. If these results agree with ECoG, the standard clinical method for brain mapping before brain resection, HR-EEG can provide a non-invasive method for pre-operative planning.

Currently, clinical EEG study (i.e. 20 or fewer electrodes) and structural neuroimaging are methods used to study patients who have medically intractable epilepsy for functional and anatomical abnormalities respectively. Neuroimaging helps identify pathological lesions or other focal structural abnormalities. Nuclear medicine imaging techniques, such as SPECT, are sometimes used together with EEG to study the nature of the underlying pathology of the seizure disorder and the extent of the epileptogenic zone. Besides scalp-recorded EEG testing, more advanced techniques, such as video-EEG telemetry, are used to study more closely the clinical manifestation of the seizures of particular patients. Some patients need to undergo surgery (first stage) to insert grid electrodes before the actual brain resection (second stage). This is for monitoring their interictal and ictal cortical potentials extra-operatively for extensive periods of time to determine their epileptogenic zones before brain resection. If the epileptogenic zone determined from deblurred HR-EEG corresponds well with that from ECoG, it provides non-invasive and detailed information about the epileptogenic zone before the actual brain surgery.

For epilepsy surgery patients with no structural lesions, clinical EEG serves as the only information for positioning of subdural grids for ECoG recording. HR-EEG recording with Deblurring™ analysis may be able to provide additional information to determine where and how extensively to implant subdural grid(s) before brain resection.
5.1.1 Definition of An Epileptic Spike

Epileptiform activity is generated when depolarization of the cortex results in synchronous activation of many neurons, i.e. summation of synchronous superficial EPSPs or deep IPSPs in the cortex. The abnormality in epileptiform activity is the appearance of transient high amplitude spikes. A spike is a sharply contoured waveform with a duration of 20-70 ms and, usually, a negative polarity (Figure 26). When many pyramidal cortical neurons activate synchronously, instead of producing just a field potential in the individual neuronal level, a dipole layer is produced because they are arranged in a parallel fashion. The epileptiform activity picked up by an macro functional recording technique, such as EEG, represents the net sum of activity of a large population of synchronously affected neurons.

Depolarization of the superficial cortical layers is associated with the influx of sodium ions into the cortical cells (i.e. EPSPs). A negative field ("sink") is created in the superficial layers and a positive field ("source") in deeper layers for epileptiform activity. A dipole for this field potential has the negative end pointing towards the cortical surface, and negative spikes are recorded by scalp electrodes (Gregory & Wong, 1992; Jayakar, Duchowny, Resnick, & Alvarez, 1991). Negative spikes can also be produced by inhibitory synaptic connections in the deep layers of the pyramidal cells. The IPSPs produced within the pyramidal cells cause an extracellular current flow similar to that produced by the superficial excitatory connections.

Positive spikes can be produced by either superficial IPSPs or deep EPSPs. They are rarer than negative spikes as epileptiform activity. However, positive spikes are often seen in EEG records due to the choice of reference in the reading montage, but they are not "true" positive spikes produced by the pyramidal neurons.
FIGURE 26  A "Typical" Spike

![Graph showing a typical spike waveform with a 20-70ms interval between voltage peaks.]

FIGURE 27  Ictal Epileptiform Activity

Repetitive, rhythmic ictal pattern develops in the left frontal-central quadrant, showing bursts of abnormal discharges containing spikes or sharp waves.
Focal spikes often indicate a focal seizure disorder. Focal spikes are only diagnosed if the spike is consistent, has a definable field, and cannot be explained by artifacts (Misulis, 1993). During simple partial seizures, the EEG usually shows prominent spiking over the involved cortical area. However, not all epileptiform activity shows spiking in the EEG record; for example, if the deep layers of cortex and subcortical structures are the origins of spikes, the scalp surface electrodes may not be able to pick up the activity. In other words, there may not be sufficient amplitude to produce a spike detectable by surface electrodes.

### 5.1.2 Definition of A Seizure

An epileptic seizure is a sudden and transient paroxysmal discharge within the brain that is sufficient to cause a behavioural change detectable by the patient or an observer. A seizure can be characterized as an "electrical storm" in the brain where neurons fire involuntarily and produce a series of large amplitude spikes. A seizure can be associated with different clinical signs, depending on the brain regions affected (Bruni, Blume, Lee, Sadler, & Saint-Hilaire, 1995). For example, in some patients, posturing, jerking and staring can be seen. Because the seizure activity is involuntary, many patients cannot control their normal functions during a seizure. Some have a lapse of memory during a seizure. Patients often have compatible functional deficits within the locations of their epileptogenic zones. An EEG recording during a seizure shows the ictal epileptiform activity of a patient in Figure 27. By studying the onset of focal seizure activity, the origin(s) or source(s) of the seizure can be localized by electrophysiological mapping.
5.1.2.a Terminology of Seizure

Ictal activity refers to EEG activity recorded during a seizure. Interictal activity refers to abnormal EEG activity recorded between two seizures. Epileptiform activity is EEG activity related to epilepsy, which includes features such as spikes, delta waves, and rhythmic patterns of spike-and-slow-wave. The mapping of seizure activity is to identify the epileptic focus, which is an electrophysiologic concept corresponding to the locations of maximum ictal or interictal epileptic activity (Engel, 1990). The mapping of the seizure onset activity identifies the brain tissues necessary for generating epileptic seizures, i.e. the epileptogenic region.

5.1.2.b Definition of the Epileptogenic Zone

The epileptogenic zone refers to the cortical area responsible for generating epileptiform activity in a patient. In focal epilepsy, seizure activity originates from one cortical region, manifests and propagates itself to a larger area, sometimes even the whole hemisphere. The epileptogenic zone is the focus of the generator for the ictal activity at the onset of a seizure.

5.2 Objective and Significance

Pre-surgical brain mapping by both HR-EEG with Deblurring™ and ECoG on 2 pediatric patients will be presented here. For the first subject, SEP mapping of index fingers recorded non-invasively by HR-EEG was compared with intra-operative ECoG ulnar nerve stimulation results. For the second subject, activity at ictal onset as well as SEP recorded by HR-EEG with Deblurring™ method was compared with extra-operative ECoG results obtained during intensive monitoring of this patient before her epilepsy surgery. The comparison between deblurred HR-EEG data and the ECoG data is an initial attempt to determine the accuracy or external validity of Deblurring™ and the clinical value gained by using this technique as a part of the pre-surgical mapping evaluation for brain surgery patients.
Intractable seizures may be defined as an "unacceptable number of epileptic attacks despite medical and sociopsychologic management, or seizures that can only be eradicated by toxic levels of antiepileptic drugs" (Blume, 1992). Intractable seizures may occur in patients with complex partial seizures, secondarily generalized seizures or multiple types of seizures. Epilepsy surgery may be considered in adults or children afflicted with chronic, medically refractory, partial or secondarily generalized seizures. Cortical resection may be considered when the origins of all or most seizures can be localized to one cerebral focus and that the epileptogenic zone can be removed without significant neurologic impairment. In order to achieve good surgical outcome, the resection of the epileptogenic zone must affect normal functions as little as possible.

Brain mapping studies on brain surgery patients allow an invaluable opportunity that is not present in the general population. These patients will have surgical mapping by ECoG and electrical stimulation before their brain resections. Therefore, results of the computed cortical EEG by Deblurring™ can be compared with real cortical recording, representing a unique opportunity to validate Deblurring™ results. The following two studies involved direct comparison of the results of deblurred HR-EEG with ECoG.
5.3 Study P-1: Mapping of the Primary Somatosensory Cortex in a Pediatric Patient with Cavernous Angioma by HR-EEG and Intra-operative Electroencephalography

This patient study allowed the comparison of the mapped SEP response area by the deblurred HR-EEG data with the subdural SEP response area mapped clinically in the operating room by the epilepsy surgery team. The procedure for intra-operative somatosensory mapping was not identical to the SEP protocol presented in Section 4.2. This study provided the first available data for direct comparison between the estimated and measured cortical potential during somatosensory stimulation in our research laboratory.

5.3.1 Study Procedure

5.3.1.a Subject

Patient AV001 was a 12-year old right-handed girl with partial seizures and left hemiparesis. Clinical MRI showed right central cavernous angioma (CA). CA is a congenial vascular anomaly of the nervous system and is formed by large vascular spaces compartmentalized by prominent fibrous wall (Rubin & Farber, 1999). The patient was to undergo resection of the vascular malformation with intra-operative ECoG for determining motor and somatosensory functional areas. Mapping by HR-EEG with steady-state SEP protocol was performed one week before surgery. The results would be compared with the clinical ECoG data obtained in the operation room during the resection of the angioma. The patient’s parents (and the patient) gave consent to participate in the HR-EEG study. The study was conducted with the approval of the UBC and the BC’s Children’s Hospital research review committees. This research study did not influence clinical decisions needed to be made for this case. Data from this study have been included in a poster presentation by Bjornson, Giaschi, Cochrane, Au Young, & Rootman et al.(1999).
5.3.1.b Anatomic MRI Acquisition

The structural MRI set used for constructing the realistic head model was acquired one day after the HR-EEG study. The patient’s head was scanned sagittally at the BC’s Children’s Hospital with voxel size 1.5mm x 1.5mm x 1.5mm (TR22ms/TE4.4ms/FOV 38.4cm/flip angle 30deg/thickness 1.5mm/matrix 256x256).

5.3.1.c SEP Recording by HR-EEG

A SEP study protocol similar to that used for Study A-2 (Section 4.2.3C) was adopted. A 128-channel child size Electro-Cap was used for this study. The reference was tied ear electrodes. The ground was placed at the nasion. The electrical stimulus was a 0.2ms pulse delivered at a frequency of 13.7Hz by ring electrodes on the finger by the Neuropack 4 Mini EP machine (Nihon Kohden, Japan). The stimulation time points were labelled by a marker generator in an extra EEG channel by 15ms-long pulses. Two 180s trials were performed: one was for stimulation at the left index finger and the other was for stimulation at the left thumb. The patient maintained her gaze towards a fixation spot at 1m in front of her during the stimulation. The stimulation was set at about 4 times the sensory threshold, which for this patient was 4.2mA.

5.3.1.d Clinical SEP Recording by ECoG

Intra-operative SEP recording results were used to compare with the deblurred HR-EEG results. This part of the experiment was performed by the epilepsy surgery team for clinical purposes using the Nicolet Viking IV EP machine (Madison, WI, USA). Since the patient’s CA was in the right central region, grid electrodes were placed at the right hemisphere and hence left finger stimulation was performed.
The intra-operative SEP data were obtained using a 4x5 grid of subdural surface contact electrodes spaced 10mm apart and placed on the right central region. Intra-operative photographs were taken to allow off-line alignment and co-registration of the grid location with the realistic head model. The location of the grid placed on the patient’s segmented cortical surface is shown in Figure 28. The top view was chosen to minimize alignment errors due to scaling and orientation angle of the 3-D head models. A small exposed cortical surface was available in the intra-operative photographs for comparing with the segmented cortical surface from the anatomic MRI, so the alignment depended mostly on the head circumference and locations of face features, such as ears and the inter-hemispheric longitudinal fissure. The cubital ulnar nerve was stimulated by 0.2ms electrical pulses at 4.7Hz and 500 trials were collected to get an averaged SEP waveform. SEP phase reversal identification method was used to localize the sensory area by the epilepsy surgery team. This method involves identification of the N20 and P30 peak in the averaged SEP in the somatosensory cortex and an approximate mirror-image waveform consisting of P20 and N30 in the motor cortex. Polarity inversion of these potentials across the central sulcus is a major criterion (Allison, 1987; Cakmur et al., 1997; Cedzich et al., 1996; Lesser et al., 1987). The identified electrode contacts were then marked on the co-registered head diagrams.
FIGURE 28  Location of Subdural Grid for Patient AV001

(A) ANTERIOR  POSTERIOR

(B) The caverous angioma (CA) was anterior to the central sulcus (Sc) in the right central cortex.

The subdural grid was positioned over the caverous angioma (CA), mostly anterior of the central sulcus (Sc).
5.3.1.e Data Analysis

Cortical Surface Segmentation

The realistic head model was constructed from the patient's anatomic MRI. The cortical surface was segmented from the MRI and a 3-D brain was rendered from the images (Appendix 1). The segmented brain was orientated to top view and exported to PhotoShop 4.0 (Microsoft, WA, USA) for image processing to allow superimposing of images of grid location, deblurred and ECoG results.

HR-EEG Data

One deblurred topographic map was made for each finger stimulation. The electrode positions were co-registered onto the patient's head model. The HR-EEG data were edited and filtered with a bandpass of 1-50Hz before analysis. Channels with artifacts were removed before data analysis, namely, F455, F355, P255, P155, O155, O255, P455, PO2, and PO1. The data were analyzed by the signal synthesis technique similar to Study A-2. The positive response in the contralateral central area was the peak to be mapped in the topographic maps. The extracted signal then was processed by Deblurring™ to compute the estimated cortical SEP. A 3-D topographic voltage map was computed at the time the positive maximum response was recorded in the peak channel, which was determined in a similar way as for Study A-2. The colour scale was adjusted by thresholding to allow regions with 50% and above of the maximum amplitude to be visible in 10% increment steps in each 3-D deblurred topographic map. For each finger stimulation, the deblurred topographic map was orientated to the top view and scaled to allow co-registration with the ECoG results on the segmented brain surface in PhotoShop. The deblurred and the ECoG mapping results would be compared for their congruency of the primary somatosensory response area.

ECoG Data

The ECoG result consisted of the electrodes where the maximum positivity and the maximum negativity occurred during intra-operative ulnar nerve stimulation. The identified electrodes were marked
on the grid location diagram and then superimposed on the segmented brain surface.

### 5.3.2 Result

The exact stimulation frequency was determined from the power spectrum of the marker channel. By using signal synthesis, the 13.715Hz and 27.429Hz components were extracted from the raw data.

Figure 29 shows the functional mapping results for this patient. HR-EEG with Deblurring™ localized the response area for the left thumb stimulation (A) and the left index stimulation (B) at the right central region. The ECoG data showed a phase reversal at the contacts labelled "+" and "-" during right cubital ulnar nerve stimulation (A and B). The mapped regions by HR-EEG with Deblurring™ and ECoG were both located in the right central cortex but did not overlap each other. In both index finger and thumb stimulation, the areas mapped by HR-EEG were more anterior. In the deblurred HR-EEG results, a secondary midline frontal response with lower amplitude was also mapped. No grid electrodes were used in that area during intra-operative recording.
Thresholding of the colour scale was done individually in each deblurred map to show only the mapped area with an averaged evoked response at 50%+ voltage (µV) of the highest averaged positive evoked peak amplitude recorded in the contralateral post-central region in each finger stimulation. Each map represents deblurred voltage activity at the time of the apex of the selected peak component of a left finger stimulation trial of patient AV001.

**A**

**LEFT THUMB STIMULATION**

**B**

**LEFT INDEX FINGER STIMULATION**

Intra-operative Results:
SEP phase reversal is labelled with “+, -”.
Motor area is labelled with “m”.

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5.3.3 Discussion

Both methods successfully localized the sensory response area for left index and thumb stimulation at the right central cortex. However, the deblurred SEP responses were more anterior than the grid data. The “+” contact for the ECoG data and the centres for the deblurred activity for left thumb and left index finger stimulation were about 1.5cm apart. This discrepancy may be due to the difficulty of separating response components, as discussed in Study A-2. The peaks selected for making the deblurred topographic maps may not be related to the primary somatosensory cortex activity but to secondary areas such as the motor cortex. The P30 and P50 peaks of a typical averaged SEP are located in the parietal area, but the P22 peak is located in the frontal area. The motor cortex as well as the medial central cortex are parts of the human brain related to some components of the SEP. There is a need to select only the response components for the primary somatosensory cortex for more specific HR-EEG mapping. N20 component is the clinical choice for mapping the primary somatosensory cortex. The ECoG data for this study, on the other hand, looked specifically at the N20 component in the post-central cortex and the mirror P20 component in the pre-central cortex for mapping the somatosensory cortex, the central sulcus, and the primary motor cortex.

Support for the mapping of a pre-central peak rather than a post-central peak was available from the data itself (Figure 30). When the responses for left index finger stimulation were displayed with a full-range voltage scale, i.e., without thresholding to display only the positive peak voltage, the evoked potential had a voltage distribution with a positive peak in the pre-central region and a negative peak in the post-central region. The corresponding dipole, computed by DLM using a 3-layer spherical model best fitted to the realistic head model, was located near the central sulcus with an orientation indicating a horizontal voltage distribution (Goodness-of-fit>91%). Both the voltage distribution and the dipole suggested that the selected peak for HR-EEG mapping in this subject could be the P22 peak, which was the peak expected to be recorded in the pre-central gyrus (Desmedt & Cheron, 1982).
FIGURE 30  Source Localization of SEP Peak for Study P-1

Each map represents deblurred voltage activity at the time of the apex of the selected peak component of the left index finger stimulation trial of patient AV001. The colour scale allows both positive and negative voltage activity to be visible. The dipole solution was computed by a 3-layer spherical model best fitted to patient AV001's head.
The discrepancy may also be due to abnormal cerebrovascular tissue, the CA. The CA was located in the right pre-central cortex, and it could affect the conduction of the response components from the cortex to its surface before it was recorded by the scalp electrodes. Some possible changes were amplitude and locations of these components. Deblurring™ estimates the cortical potential by modelling the thickness of the skull and scalp layers and by assuming uniform conductivity in the cortical tissues. If the vascular malformation has different conducting properties from the surrounding normal cortical tissues, the scalp-recorded EEG may be more adversely affected than the ECoG recording because the scalp electrodes were spaced less densely than the grid electrodes and, after volume conduction, more surrounding electrodes are affected by the CA. Patients that had been studied before by the Deblurring™ method in a previous SEP study did not have lesions or other brain structural abnormalities (Gevins et al., 1994).

The third reason for the discrepancy was the lower S/N ratio in steady-state than transient SEPs. High stimulation rate is related to reduced somatosensory response amplitude. Moreover, the steady-state SEP technique used a narrow bandwidth for recording; the response components were not as prominent and defined as hoped. This combination translated to a less than ideal S/N ratio in the steady-state SEP recording, and the most prominent positive peak was picked as the component to be mapped, rather than a specific clinical peak, such as the N20 component. Very few EEG machines that have the capacity of recording HR-EEG also have a wide enough recording bandwidth for SEP recording.

The fourth reason for the discrepancy was that different sites were stimulated for the HR-EEG study and the ECoG clinical testing. Further studies with the same SEP protocol for both the HR-EEG and ECoG studies can rule out the possibility that the difference in mapped cortical areas reflects stimulation sites and frequency difference.

The data suggested that the deblurred and ECoG results did not overlap, but it was not clear whether this was due to the inaccuracy of the Deblurring™ process, the procedural errors in the HR-EEG
protocol, or to the difference in protocols between HR-EEG with Deblurring™ and ECoG. To allow better comparison of the Deblurring™ method with ECoG, the same SEP protocol should be used in future for both HR-EEG and ECoG studies. Moreover, the S/N ratio and the selection process of the response components need to be improved to allow a more defined peak to be mapped within each method.
5.4  **Study P-2: Study of the Primary Somatosensory Cortex and Epileptogenic Zone in a Medically Refractory Seizure Patient by HR-EEG and Extra-operative Subdural Recording**

In this study, the patient underwent grid implantation in a craniotomy and then monitored by video-telemetry and ECoG extra-operatively for seizure activity in the neuroscience ward for an extensive period of time before brain resection. This allowed a SEP study with the same stimulus parameters and recording parameters as the HR-EEG with Deblurring™ study to be conducted with ECoG recording. The same stimulation sites could also be used for both methods. The deblurred HR-EEG data and the ECoG data could then be subjected to the same analytic procedure for extracting the SEP signals. Seizure activity would also be studied. Ictal spikes have a better S/N ratio and longer duration which should be adequate to be recorded by the existing recording bandwidth.

**5.4.1  Study Procedure**

**5.4.1.a  Subject**

Patient PS001 was a 12 year old right-handed girl with medically refractory seizures arising from the left frontal lobe based on the clinical EEG evaluations. No lesions were shown in previous clinical MRI evaluations. After the patient was identified as a possible epilepsy surgery candidate and the ECoG recording was scheduled, she was referred for participation in this experiment. The patient's parents (and the patient) gave informed consent for participating in the experiment.

The pre-surgical plan for this patient was to map the epileptogenic zone and functional areas by grid electrodes extra-operatively during an extensive seizure monitoring period before the actual resection surgery. The research plan was to have the patient's seizures and SEPs studied by both HR-EEG and ECoG. The study was approved by the UBC and the BC's Children's Hospital research ethics committees.
5.4.1.b Anatomic MRI Acquisition

The structural MRI for this patient was acquired for clinical evaluation at the BC's Children's Hospital 3 months before excisional surgery. The MRI set was acquired in the coronal orientation with voxel size 1.5mm x 1.5mm x 1.5mm (TR22ms/TE4.4ms/FOV 38.4cm/flip angle 30deg/thickness 1.5mm/matrix 256x256).

5.4.1.c SEP and Ictal Recording by HR-EEG

Two HR-EEG studies were performed on the patient. The first HR-EEG study was performed 7 months before excisional surgery; the second, 2 months before excisional surgery. Study 1 involved only seizure recording. Study 2 involved SEP and seizure recording.

A 128-channel child-size Electro-Cap (Neuroscan, Inc., Sterling, VA, USA) was used for acquiring the HR-EEG data. In study 1, the reference was tied mastoids. In study 2, the reference was tied earlobes. This change was done to reduce muscle artifacts in the EEG data during seizures. In both studies, the ground was placed at the nasion.

In the SEP mapping study, the right fingers were stimulated by 0.2ms electrical pulses applied by ring electrodes and delivered by the Neuropack 4 Mini EP machine (Nihon Kohden, Japan). The stimulation frequency was at 13.715Hz. The stimulating current intensity was set to be 7.2mA, which was three times the patient's sensory threshold. The fingers studied were the right thumb, the right index, and the right middle fingers. The stimulation time points were labelled by a marker generator in an extra EEG channel by 15ms-long pulses.

For capturing seizure activity, spontaneous HR-EEG was recorded as outpatient video-telemetry recording during the second HR-EEG study session. When a seizure occurred, the patient's parents or an EEG technologist pressed the alarm button and the time for the seizure was recorded by the EEG machine.
5.4.1.d SEP and Ictal Recording by ECoG

Grid Location

An 8x6 grid (G1) of subdural surface contact electrodes spaced 10mm apart was placed over the epileptogenic zone determined from clinical scalp EEG testing. A smaller grid (G2, 5x2) and strips (S1, S2, S3) of subdural electrodes were placed around this main grid. Only data from the two grids (G1 and G2) were included for analysis (Figure 31). An intra-operative photograph was taken to show the location of grid electrodes for subsequent alignment with the anatomic head model.

Extra-operative Recording

Because subdural EEG monitoring (i.e. ECoG recording) and video-telemetry were performed for a few days to record ictal activity after craniotomy, SEP mapping with ECoG recording could be performed extra-operatively in the ward. This allowed the exact SEP protocol, as the HR-EEG experiment, to be used to record grid SEP. The recording EEG machine was the Telefactor Beehive System (West Conshohocken, PA, USA) for both ECoG and HR-EEG data acquisition. The sensory stimulation could be better controlled outside the operative environment. The only minor difference was that subdural SEP mapping was performed with patient’s eyes half-closed rather than open due to face swelling post-operatively. The electrical pulses were generated by the Viking IV EP machine (Madison, WI, USA) with the exact same stimulus parameters as the HR-EEG study. Right finger stimulation (thumb, index, and middle finger) was performed.

The procedure for capturing epileptic seizure activity was identical between the ECoG and the HR-EEG recording.
Subdural grid was located in the LEFT FRONTAL-CENTRAL CORTEX.
5.4.1.e Data Analysis

Cortical Surface Segmentation

The realistic head model was constructed from the patient’s anatomic MRI. The cortical surface was segmented from the MR slices and a 3-D brain was rendered from the segmented images. The segmented brain and the realistic head model were then orientated to a 30°-angled side view (from the vertical) to provide a good view of the left hemisphere where the grid electrodes were placed. The brain images were then imported into Photoshop 4.0 (Microsoft, WA, USA) for image overlaying. The grid electrodes were aligned and positioned on the cortical surface by comparing the sulcal anatomy available on the intra-operative photograph and the segmented brain.

HR-EEG: SEP Data

SEP data were analyzed by signal synthesis similar to that done for Studies A-2 and P-1. Three separate deblurred voltage maps were made to show the location of the highest response peak for each right finger stimulation. The full-width 50% area (with 10%-increment steps) was coloured in each map for visualization of the response area (as in Study P-1). The topographic maps were orientated and scaled to match the head model and the segmented brain for overlaying.

HR-EEG: Ictal Onset

Two seizures were recorded (seizure-A and seizure-B). Seizure-A was recorded during the first HR-EEG study session (Study 1) and seizure-B, the second HR-EEG study session (Study 2). Ictal onset for each seizure was identified by experienced EEG technologists. This patient had negative ictal spikes in the left frontal-central region. Each ictal data set was first digitized from the ictal onset to the post-seizure activity suppression period. Negative spikes were selected from the recording at seizure onset. All spikes that occurred from the ictal onset to the beginning of a rhythmic ictal pattern or the manifestation of behavioural signs were selected from the recording. These spikes were selected and classified as “focal” spikes because they occurred at the ictal onset before the seizure activity spread and
become more sustained. Eight consecutive focal spikes were selected from seizure-A recording and seven from seizure-B recording. A post-hoc filter was set to be 1-35Hz to correct DC-offset and muscle artifacts before averaging. Artifact channels also were removed (FC5, FT9, P6, O10 for seizure-A and FC5 for seizure-B). Averaging was applied on the selected spikes for each seizure. Then, Deblurring™ was applied to enhance the averaged spike. Deblurred ictal potential maps were made at the time of the peak of the averaged negative spike for each recorded seizure. Colour scale was set to show the full width 50% maximum with 10%-increment steps. The topographic maps were orientated and scaled to match the head model and the segmented brain for overlaying.

**ECoG: SEP Data**

The subdural SEP data were first digitized and filtered (bandpass 1-50Hz). The SEP signal was extracted and averaged by signal synthesis. Then, x-y plots were made to show the averaged SEP response recorded in each electrode. Electrodes which showed responses were identified and marked on the grids for comparison with the deblurred HR-EEG results.

**ECoG: Ictal Onset**

One subdural grid seizure was included for analysis (seizure-grid). Ictal onset was identified by experienced EEG technologists. Negative spikes were selected from the recording from ictal onset to the beginning of a rhythmic ictal pattern or manifestation of behavioural signs the same way as the HR-EEG recording. A post-hoc filter was set to be 1-35Hz. Twelve consecutive focal spikes were selected from the subdural ictal recording. One noisy channel, G1-33, was identified in the recording and excluded. Averaging was applied on the selected spikes. The channels showing averaged spikes were picked as channels involved in generating ictal activity and considered as part of the epileptogenic zone. These involved electrodes then were marked on the cortical surface of the segmented brain for subsequent comparison with the deblurred seizure results.
5.4.2 Result

5.4.2.a SEP

The exact stimulation frequency was determined from the power spectrum of the marker channel. By using signal synthesis, the 13.715Hz and 27.429Hz components were extracted from the raw data of both HR-EEG and ECoG data. The waveform of the averaged deblurred SEP response for the right index finger stimulation is shown in Figure 32. The response area for the right thumb was in close proximity to this mapped region (Figure 34A).

FIGURE 32 Deblurred SEP for Right Index Finger Stimulation for Study P-2
The waveform for the averaged subdural SEP response for right index finger stimulation is shown in Figure 33A. Figure 33B shows the location of the index finger area mapped by the subdural SEP recording on the cortical surface. Figure 34 shows the primary somatosensory cortex mapping results of both methods superimposed upon each other for all three digit (thumb, index, and middle) stimulation. The deblurred maps for the HR-EEG data showed peak activation in left post-central cortex for both right thumb and right index finger stimulation. The right middle finger stimulation yielded activation in a more medial central area. The activation for the right middle finger stimulation had the highest amplitude when compared with the activation for the right thumb and the right index finger stimulation.

The subdural SEP results were concentrated at the posterior end of the grid for all three finger stimulation. The involved grid channels included G1-14, G1-15, G1-16, G1-24, G1-25, G1-26, G1-30, G1-31, G1-32, G1-39, and G1-40. All the involved channels lie in the post-central cortex. The ECoG results for right thumb stimulation and right index finger stimulation matched with the deblurred results of the same stimulation when the two mapping results were overlaid upon each other in the composite diagrams.
FIGURE 33 Subdural Grid SEP for Right Index Finger Stimulation for Study P-2

(A) G1-1 G1-2 G1-3 G1-4 G1-5 G1-6 G1-7 G1-8
  G1-9 G1-10 G1-11 G1-12 G1-13 G1-14 G1-15 G1-16
  G1-17 G1-18 G1-19 G1-20 G1-21 G1-22 G1-23 G1-24
  G1-25 G1-26 G1-27 G1-28 G1-29 G1-30 G1-31 G1-32
  G1-33 G1-34 G1-35 G1-36 G1-37 G1-38 G1-39 G1-40
  G1-41 G1-42 G1-43 G1-44 G1-45 G1-46 G1-47 G1-48

(B) Right index finger area mapped by subdural grid
Thresholding of the colour scale was done individually in each deblurred map to show only the mapped area with an averaged evoked response at 50%+ voltage (µV) of the highest averaged positive evoked peak amplitude recorded in the contralateral post-central region in each finger stimulation. Each map represents deblurred voltage activity at the time of the apex of the selected peak component in a right finger stimulation trial of patient PS001.

A

RIGHT THUMB STIMULATION
○ = Right thumb area mapped by subdural grid

Voltage (µV)

B

RIGHT INDEX FINGER STIMULATION
○ = Right index area mapped by subdural grid

Voltage (µV)

C

RIGHT MIDDLE FINGER STIMULATION
○ = Right middle area mapped by subdural grid

Voltage (µV)
5.4.2.2 Ictal Onset

In all recorded seizures (seizure-A, -B, -grid), the epileptogenic zones were localized to the left anterior quadrant. This was consistent with results from previous clinical EEG examination. The topographic maps for the two deblurred seizures (seizure-A and seizure-B) are shown in Figures 35A and 35B. Seizure-A and seizure-B had different deblurred topography. The extent of the topography was different. Seizure-A spread towards the left frontal temporal area and a secondary area was mapped to the left parietal region. Seizure-B spread mostly towards the frontal medial area.

Channels identified as involved for generating spike activity in the subdural grid seizure (seizure-grid) were marked in Figures 35A and 35B. The involved subdural grid channels were: G1-1 to G1-5, G1-9 to G1-13, G1-17, G1-20, G1-21, G1-25 to G1-28, G1-34, G1-35, G2-4, and G2-9. The full-width 90% maxima (i.e. red areas in Figures 35A and 35B) of the deblurred averaged spike activity for seizure-A and seizure-B lay near G1-4 (i.e. the marked electrode in Figure 36B), which recorded the most negative averaged spike among all the subdural grid electrodes. Therefore, there was some congruence between the deblurred and the ECoG ictal onset mapping results.
Thresholding of the colour scale was done individually in each deblurred map to show only the epileptogenic zone with an averaged spike peak 50%+ voltage (µV) of the most negative averaged spike recorded. The map represents deblurred voltage activity at the time of the apex of the most negative averaged spike in a seizure event of patient PS001.

**A**

**SEIZURE-A & SEIZURE-GRID**

○ = Seizure onset mapped by subdural grid

-120 \[\text{Voltage (µV)}\] 0

**B**

**SEIZURE-B & SEIZURE-GRID**

○ = Seizure onset mapped by subdural grid

-130 \[\text{Voltage (µV)}\] 0
FIGURE 36  The Location of the Most Negative Subdural Seizure Activity for Study P-2

A  SEIZURE-GRID AVERAGED WAVEFORM

- = Seizure onset mapped by subdural grid

B  LOCATION OF EPILEPTOGENIC ZONE

- = most negative spike
○ = Seizure onset mapped by subdural grid
5.4.3 Discussion

5.4.3.a SEP

In this study, the same stimulation protocols were used in both the HR-EEG and the ECoG mapping sessions. This was the first case in our laboratory, which was studied by both HR-EEG and ECoG with a matched protocol. The comparison between the averaged SEP collected by deblurred HR-EEG and that by ECoG is rare in the literature, especially for the pediatric population. The only reported study was by Gevins et al. (1994) in two adult patients. Difficulties in conducting these studies were due to the requirement of the coordination of many clinical departments to collect a complete set of data, the small number of available patients in a single hospital, and the infancy of HR-EEG mapping with realistic head models and Deblurring™. In order to co-register the deblurred data and the ECoG data together in one 3-D structure for visualization, the patient’s high resolution 3-D T1-weighted MRI data must be available for segmenting the cortical surface to make a 3-D brain model. This model serves as the structural base for superimposing functional data. In order to co-register the functional data, the coordinates of scalp electrode positions and grid positions must be collected by 3-D location digitizers. This step is an additional step to regular clinical EEG and ECoG studies. Therefore, the minimum set of data needed for this kind of study includes a pre-surgical high-resolution 3-D T1-weighted MRI, HR-EEG data, 3-D electrode positions, intra-operative photographs (before and after grid placement), ECoG data, and post-surgical high-resolution 3-D T1-weighted MRI. All these data must also be collected within a limited time frame, which required proper scheduling, planning, and coordination from a central research study group, and cooperative efforts between departments to provide the combined results.

In the Gevins' et al. study (1994), an initial empirical validation of the Deblurring™ method was performed by comparing, for two patients, SEPs recorded from a 64-channel grid (8 X 8) over the somatosensory cortex to deblurred SEPs. Their finding showed that there was a good concordance between the topography of the deblurred data and the ECoG data. However, they suggested that a denser
scalp montage was needed in future Deblurring™ validation studies since the grid data were more densely sampled than the HR-EEG data. In our study, a 48-channel grid (G1, 8 X 6) and a 10-channel grid (G2, 5 X 2) was placed in the left somatosensory cortex to record both SEP and seizure. The present result showed agreement with Gevins’ conclusion.

The waveforms for the deblurred and the subdural averaged SEP responses were different in form and latency in Figures 32 and 33A. The peak was more significant and larger in the subdural SEP than the deblurred SEP. Moreover, the subdural response was more focal. This suggests that the Deblurring™ model was not perfect in computing the virtual cortical potential and has room for improvement. The difference in latency between subdural and deblurred SEP could be due to difference in phase for cutting EEG files into EP epochs before averaging. Volume conduction occurs at the speed of light and should not be accounted for the latency difference between subdural and deblurred SEP. Caution is required when trying to interpret the deblurred waveform. It should not be handled similarly to scalp EEG waveform nor ECoG waveform because it is neither of them. Rather it is a spatially enhanced and modified EEG dataset with signal and noise voltages adjusted to match the estimated cortical level, so that the signals or EEG features of interest can stand out for easier identification. The inherent EP morphology differences between subdural and scalp recording, such as sharpness of the peak components, are not corrected directly by Deblurring™.

The deblurred results for middle finger stimulation showed activity in the medial central area which may be explained similarly to results for Study P-1. A secondary response area, but not the primary sensory cortex, was mapped. The other two deblurred maps provided encouraging results of being congruent with the subdural grid results. However, the centres did not lie in an exact same spot (about 1-2cm apart) although there was considerable overlap of the mapped regions. This study was an improvement from the previous patient study (Study P-1) because the same stimulation sites and frequency were used. A larger cortical surface also was available to align the grid positions on the
segmented brain for improved accuracy. Therefore, the offset between the two results due to co-registration error was reduced.

The need to improve the steady-state SEP protocol remains: a specific SEP peak should be chosen for comparison of the primary sensory mapping results to rule out the possibility of mapping other brain regions related to SEP. Gevins and colleagues also reported difficulties of obtaining an averaged SEP with a good S/N ratio in their HR-EEG study (1994). Their recording bandwidth (up to 100Hz) was similar to the recording system used for studies in this thesis.

This SEP study shows that there was good agreement between the deblurred results and the ECoG results. The low S/N ratio of the steady-state SEP data remained a challenge for successful mapping of the primary sensory cortex.

5.4.3.b Ictal Onset

Mapping ictal spikes from this seizure patient with a high-density electrode montage, realistic head model, and Deblurring™ was unique. Indeed, this was the first published record of using this HR-EEG technique for identifying the epileptogenic zone (Gevins et al., 1999). A recent study, however, has been published to compare mapping of the epileptic foci by MEG and that by ECoG. (Otsubo, Sharma, Elliott, Holowka, & Rutka et al., 1999).

The spike waveform could be quite regular within a subject, providing consistent “signals” for averaging and mapping. Mapping averaged ictal spikes has its pros and cons. One advantage is that ictal spikes have a more satisfactory S/N ratio than evoked potential peaks and only a few are needed to make an averaged spike with significant signal level. Moreover, artifacts affect the averaged spike less than individual spikes, reducing chances of mapping error. The disadvantage is that the early spikes and the late spikes can have very dissimilar topography due to propagation of the electrical activity and recruitment of secondary areas in generating the epileptic behavioural symptoms. Therefore, it was
important to limit the selected spikes to the ones at the onset of an epileptic event, as was done in this study, so that only the onset zone was mapped. This also reduced the effect of artifacts related to movement and muscles on the signal.

In this case, the most negative averaged spike activity of seizure-A, seizure-B and seizure-grid was recorded in a similar location (near to G1-4). The extents of the mapped epileptogenic zones, however, were different. Even the topographies for the two deblurred seizures were different. Seizure-A and seizure-B were recorded in separate HR-EEG study sessions, but this should not be the cause of the discrepancy as the measured electrode positions from each study were used to make the co-registered diagram for each seizure. Instead, this may reflect multiple propagation routes for a single seizure generator or source in separate seizure events, or multiple generators for separate seizure events. In other words, there could be subtypes of activity generating by one single source or there could be two or more epileptogenic zones. Previous clinical EEG studies on this patient suggested that there were two subtypes of seizure events for this patient. Because the most negative averaged spikes were recorded in a similar location (near to G1-4) in seizures-A, -B, and -grid in this study, the results further strengthened the clinical observation that there was only one epileptogenic zone for this patient, but multiple propagation routes, resulting in different topographic patterns. Investigations with dipole localization using a realistic head model might help to understand the epileptic source and epileptic activity propagation pattern of this patient even further (Roth, Ko, von Albertini-Carletti, Scaffidi, & Sato, 1997).

The deblurred epileptogenic zones were much more extensive than the subdural epileptogenic zone. The subdural epileptogenic zone was more defined, more focal and spread less to surrounding electrodes. This showed that the subdural data had higher spatial resolution than the deblurred data. Besides differences between seizure events, this discrepancy could be contributed by two other factors: the spatial density of the recording electrodes and the accuracy of spatial improvement by Deblurring™. The subdural grid electrodes were 1 cm apart and record electrical activity directly on the brain's surface.
For this study, the averaged scalp inter-electrode distance was measured to be 2.56cm, and after Deblurring™, the projected inter-electrode distance just above the superficial cortical surface was 2.27cm. There was a spatial resolution difference between the deblurred data and the grid data starting at the data acquisition stage. This problem was also noted by Gevins et al. (1994), and they tried to reduce the spatial resolution of the subdural grid SEP data to match with the deblurred results in order to validate Deblurring™. This step was not done in this study for two reasons. First, this difference in spatial sampling density is one factor that can affect future clinical application of the HR-EEG technique. It is important to compare the best obtainable results by ECoG and by HR-EEG with the current protocol to consider the clinical potential of applying HR-EEG with Deblurring™ in mapping the epileptogenic zones. Second, this thesis tried to validate the existing Deblurring™ algorithm by looking at the congruency with results from other functional mapping methods. The objective was not optimizing and validating the Deblurring™ algorithm as a spatial improvement technique as Gevins et al. were doing.

The clinical method for determining the epileptogenic zones involves identification of electrodes with the earliest epileptic spikes in the ECoG recording. No numerical or statistical analysis is usually used. A similar method was used in this study to determine the timing of the seizure onset; in addition, the extents of the epileptogenic zones were determined from the averaged epileptic spikes by their relative amplitude between channels in the topographic maps. Then, the realistic head model was used for coregistration of the subdural grid and the mapping results. It is possible to make topographic maps from the subdural grid data. However, this was not done for two reasons. First, the S/N ratio of the subdural seizure activity is better than that for scalp seizure activity, and the grid electrodes are denser than scalp electrodes, such that much spatial information of the subdural seizure onset can be drawn quite readily from the waveform. Second, the subdural grid seizure activity is more localized and focal as the activity is recorded before volume conduction. The subdural activity is not lowpass filtered by the skull and hence less smooth than scalp data. The difference in spike amplitude between neighbouring electrodes
can be quite sharp. The topographic patterns for averaged subdural spikes can be so unsmooth that no extra information can be gained by interpolation. Therefore, the display of the subdural seizure activity in topographic format may not provide as much benefit as that for the scalp or deblurred seizure activity.

There were also difficulties for conducting scientific studies, in addition to the clinical presurgical evaluation, in a hospital setting. One challenge of this kind of study is the scarcity of suitable patients. For example, the patients need to go through many clinical tests prior to the epilepsy surgery and may not be available for the scientific study due to time conflicts. Another challenge is the proper coordination of many clinical departments to collect the full set of scientific data, which include a 3-D whole-head MRI, the measurement of scalp electrode positions, the HR-EEG data, the measurement of subdural grid positions, operative photos of pre- and post-grid insertion, and the ECoG data. One example is that a pre-surgical 3-D high-resolution MRI set was not available for making realistic head model on one subject whose HR-EEG data were available; thus, the data could not be used. The primary objective of the clinical departments is to collect clinical data; and their role in the scientific study should be one for providing assistance in data collection. The research laboratory should be responsible for the study planning and data analysis. However, the research laboratory cannot plan research studies when available patients are not referred to the laboratory early enough to allow all data to be collected. Using clinical data are not sufficient for conducting this HR-EEG study because information extra to a routine clinical EEG recording, such as measured electrode positions and a 3-D MRI set, is needed. Moreover, confounds need to be properly controlled during data collection.
CHAPTER 6
OVERALL CONCLUSIONS

6.1 Conclusions of Adult Volunteer Study Results

6.1.1 Study A-1: Primary Visual Cortex Mapping

The objective of this study is to determine whether HR-EEG with Deblurring™ can localize regions in the visual cortex activated by right and left visual hemifield stimulation and how the results compare to fMRI mapping with the same stimuli. Because each individual's realistic head model used for HR-EEG mapping was rendered from his or her anatomic MRI set, and the fMRI data were aligned to the anatomic MR slices, data between HR-EEG and fMRI could be compared by visualization of the results directly. The use of realistic head models enhances, especially, the within-subject comparison between mapping results by Deblurring™ and fMRI.

If the fMRI and deblurred HR-EEG mapping results converge, this can provide evidence for the accuracy of HR-EEG. The results showed that there was concordance; but in some subjects, HR-EEG mapped the activated region to both occipital lobes or just the ipsilateral occipital lobe, and not exclusively the expected contralateral occipital lobe. The difference between the fMRI data and the deblurred data in Study A-1 can be explained by the fact that the topographic maps showed surface activation, whereas the fMRI maps showed the 3-D location of the activated region(s). Deblurring™ localizes the scalp potential to the cortical surface, and fMRI localizes to the source region. If the source is superficial, then the location of the maximum activity on the surface can be very close to the location of the source. However, the maximum activity on the surface can be distant from the generating source, if the source is deep. The comparison of dipole sources and fMRI data may be more appropriate. Deblurring™ might be able to act as a spatial enhancement tool for cleaning up the scalp-recorded HR-EEG before the data are subject to the source localization algorithm.
The paradoxical lateralization phenomenon reported in the VEP literature since the late 1970's could explain the results obtained from this study. Medial surface VEP activity can be picked up by scalp electrodes in the ipsilateral hemisphere if the dipole source is orientated to project activity across the midline. Confirmation could be done by recording cortical potentials simultaneously on the medial surfaces and the occipital poles in both hemispheres, as subdural electrodes can be placed directly on the medial surface.

The study also demonstrated that there were technical difficulties to determine the thickness of the skull and to generate finite-element models for the cortical surface, the outer boundary of the skull and the scalp surface near the occipital region. Without an accurate model of the skull thickness, the present Deblurring™ method is unsuitable for visual functional studies and would give inaccurate results. Even though Deblurring™ helped to localize the activation to the cortical surface, the technical difficulties of making a good surface boundary model in the occipital region for estimating the cortical potential made it less than ideal for localizing visual activation.

Technical problems for HR-EEG, such as electrode placement locations and construction of the Deblurring™ mesh, affect the application of this process for VEP studies in the clinical population. This highlights the importance of conducting research studies like this one to investigate the applicability of the HR-EEG technique with Deblurring™, even though the Deblurring™ model was tested theoretically before.
6.1.2 Study A-2: Primary Somatosensory Cortex Mapping

The purpose of this study was to determine first, if HR-EEG was superior to routine clinical EEG, and second, if Deblurring™ improves scalp HR-EEG data. Steady-state SEP data were collected for this study because a stable Deblurring™ model could be made over the primary somatosensory cortex without technical barrier.

The scalp HR-EEG topographic map was more superior than the scalp EEG map because the same somatosensory stimulation produced a more defined response area. With more electrodes, it could reduce the chance of missing a weak response when the electrodes were not placed directly above the most active responding neurons. The details of the EEG maps improved with using a denser array of scalp electrodes, and the extra cost, time, and expertise for analyzing data from using more electrodes for clinical EEG studies is justified.

Deblurring™ improved the SEP peaks to become more focal and consistent than scalp HR-EEG. The extents of the response peak areas were significantly reduced by Deblurring™ to become more focal for the left index finger stimulation. The same trend could be observed in most trials for the right index finger stimulation.

During analysis of the SEP data, difficulties occurred in obtaining a consistent and specific SEP component for mapping. This might be due to the narrow recording bandpass and the poor S/N level, making the averaged signal extracted by signal synthesis less than ideal. Future studies should be conducted with a transient clinical evoked potential protocol using standard averaging to allow better identification of clinical significant peaks, such as N20 and P30. The collection of prominent N20 and P30 peaks is crucial for clinical mapping of the primary somatosensory cortex. The drawback of a transient protocol with averaging is that it reduces the efficiency of collection of many trials, but it allows the collection of more independent sweeps with better S/N ratio and more precise latency. Moreover, collection of transient trials and analysis with averaging is standard clinical procedure for evoked
potential laboratories. Keeping the HR-EEG protocol as similar to the existing clinical protocol as possible helps in focussing the research on the mapping value of HR-EEG technique with Deblurring™ and realistic head models, and not differences between various evoked potential signal extraction techniques.

HR-EEG with Deblurring™ improves EEG mapping by being more consistent and precise, providing evidence for the internal validity of this technique. Future studies can benefit from any improvement in the estimation of the curved surface areas of the mapped regions in the cerebral cortex and the scalp. In the present study, projected and flattened scalp areas were estimated from the 3-D topographic maps for comparison with the deblurred areas.

A Deblurring™ mesh is technically easier to be made for the central cortex than for the visual cortex. The primary somatosensory cortex for fingers also is away from the medial surface. Technical problems of applying the HR-EEG technique existed in the primary visual cortex mapping but were not as significant in the primary somatosensory cortex mapping.

This study did not provide evidence if the peak locations were accurate or not by comparing with other neuroimaging results. The scalp data were shown to be spatially enhanced by Deblurring™, but no conclusions could be made regarding how accurate the results were. A follow-up somatosensory stimulation study could be done on this subject with fMRI, for example, to allow comparison with the deblurred result for studying the accuracy or the external validity of the mapping results.
6.2 Conclusions of Pediatric Patient Study Results (Studies P-1 and P-2)

Pre-surgical brain mapping by both HR-EEG with Deblurring™ and ECoG on two pediatric patients was presented. For the first subject, SEP mapping of index fingers recorded non-invasively by HR-EEG with Deblurring™ was compared with intra-operative ulnar nerve stimulation ECoG results. For the second subject, activity at ictal onset as well as SEP recorded by the HR-EEG with Deblurring™ method was compared with extra-operative ECoG results obtained during intensive monitoring of this patient before epilepsy surgery. The comparison between the deblurred HR-EEG data and the ECoG data was an initial attempt to determine the accuracy or the external validity of Deblurring™, and the clinical value gained by using this technique as part of the pre-surgical mapping effort for brain surgery patients.

Only two patients were studied and included in this thesis. It is premature to judge the validity of Deblurring™ with such a small subject population. Based on the results presented, it is fair to say that the spatial resolution of the deblurred results did not match the real ECoG results. Even with 128 channels, the spatial resolution of HR-EEG with Deblurring™ was not as good as ECoG because the inter-electrode spacing for HR-EEG was about 2cm but ECoG was 1cm. The deblurred HR-EEG data and the ECoG data were difficult to be directly compared. For example, ECoG recording and HR-EEG recording had different amount of noise content which affected the S/N ratio. The smoothness of the peak components were also different.

The SEP studies on the two patients could be successfully mapped to the contralateral central cortex in most of the finger stimulation trials. However, the precision of the mapping was affected by the low S/N ratio of the SEP components collected and the difficulties of separating and identifying the peak components. Some discrepancies between the deblurred data and the ECoG data could be contributed by the difficulties of collecting a robust response for mapping rather than error in the Deblurring™ technique.
The epileptogenic zones mapped by ECoG and Deblurring™ overlapped. The extents of the epileptogenic zones mapped did not agree between the two deblurred seizures, and between the deblurred and the ECoG results. However, the most negative spikes were mapped very closely to one electrode location (near the G1-4 subdural electrode) on the cortical surface in all three recorded seizures. The difference between the two deblurred results could be due to difference between seizure events. Previous clinical EEG records suggested more than one type of seizures were represented in this patient. Since only few seizures were recorded, it was not possible to confirm that the differences were purely physiological or not. It is promising that the most negative spikes were mapped to one location, suggesting that the same epileptogenic zone was identified and mapped. In current clinical practice for epilepsy surgery, the extent of the epileptogenic onset zone is not universally defined. The thresholding method used in colouring the epileptogenic zone was an unbiased way to define the brain region showing the most amount of epileptic spike activity at a seizure onset. Even though the boundary of the epileptogenic zone was determined mostly by the epileptiform activity recorded, noise level in the recording also affected the extent of the mapped region. This may account partially for the difference between the deblurred HR-EEG and the ECoG results.

One key advantage of studying the epileptogenic zone in this patient by HR-EEG with Deblurring™ and realistic head models is that this method is non-invasive. For patients who have no visible lesions, EEG acts as the most important piece of information for epileptogenic zone localization. With more electrodes, more data are collected simultaneously to study these patients' seizures. With a realistic head model, the 3-D locations of the HR-EEG electrodes on a patient's head can be viewed by the epilepsy surgery team post-recording, and the epileptogenic zone can be mapped to the patient's head. With Deblurring, the epileptogenic zone can be mapped to the patient's cortex. The HR-EEG with Deblurring™ technique may prove to be helpful to determine the location of placement of electrode grids before surgery, especially for cases with no structural cortical defects, if future studies continue to show...
agreement in the mapped locations of the most negative spikes by deblurred HR-EEG and ECoG. However, more seizure data from more patients are needed to determine if the extent of the epileptogenic onset zone for the same type of seizure events in a patient is similar between the two mapping methods. Deblurred HR-EEG data before ECoG recording may be a more useful clinical tool for deciding the location and extent of grid placement before craniotomy than routine clinical EEG, such that ECoG recording can then be used more efficiently to study the seizure propagation pattern and define the extent of the seizure activity.

6.3 Contributions and Recommendations

6.3.1 Contributions

As a report of results of pilot studies, this thesis was critical of the shortcomings and technical difficulties of the HR-EEG technique with Deblurring™ in the hope of bringing awareness that the method is still relatively untested clinically, and more effort is needed for a full assessment of the clinical application of this technique.

Here are the three major contributions made by this thesis to research in the field of HR-EEG with Deblurring™:

1. The VEP study identified technical problems of making a good Deblurring™ model for the back of the head. Because of normal functional anatomy, the VEP can be hard to map by HR-EEG since the sources of activity are located along the medial cortical surface, and both the scalp and deblurred topographies may not show activity exclusively near the sources.

2. The SEP study showed that HR-EEG improved clinical EEG, and Deblurring™ further zeroed in the mapping to a more precise and focal activated region across trials. However, care is required in the use of signal synthesis to extract an averaged steady-state SEP recorded by the available EEG equipment in the laboratory, as the signal has low S/N and may not be robust.
3. The epilepsy case (study P-2) represented, so far, the only available data for direct comparison of ECoG and deblurred results for both SEP and ictal mapping with a matched protocol. This study identified that the spatial resolution of deblurred EEG is not as good as that of ECoG; however, deblurred EEG may be suitable to act as the final non-invasive mapping method before ECoG for determining the extent and location of subdural grid insertion.

6.3.2 Recommendations

Based on the results of this thesis, a larger-scale scientific study to look at both the effect of Deblurring™ and the congruence of deblurred data with other functional imaging data, is worthwhile and needed to support the application of the HR-EEG technique with Deblurring™ as part of pre-surgical evaluation for epilepsy surgery. Future studies would be expected to benefit from the following research strategies:

1. Extra coordination efforts are required to collect a complete set of experimental data in addition to (and independent of) the clinical data required for pre-surgical clinical evaluation.

2. The use of a transient protocol with averaging for evoked potential studies, as well as a wider recording bandwidth, will allow a more stable and robust averaged EP to be collected for mapping.

3. A matched protocol for mapping with different functional imaging methods is required for comparison of the results. It is, therefore, beneficial to make the experimental protocol as similar to the existing clinical protocol for ECoG as possible. For example, the protocol could include transient EP stimulation, averaging analysis, and mapping of SEP with clinical significant peaks such as N20 and P30.

4. The thesis compares the mapping results of various functional imaging methods by superimposing them into a combined diagram. This is a simple, yet direct, method for visualizing
the congruency of the results. This presentation method requires accurate co-registration of topographic maps, fMRI images, 2-D sulcal surface diagrams, and 3-D head models. In addition to functional mapping skills, skills in manual segmentation, image processing, and knowledge of the anatomy are required to successfully co-register the images. A separate research effort to improve the quantitative analysis of the multi-modal functional mapping results, for example between deblurred HR-EEG and ECoG data, or between deblurred HR-EEG and fMRI, would benefit this current project even further.

HR-EEG technique with realistic head models allows co-registration of data with other functional mapping results. By recording with more electrodes, a more defined brain region was mapped. By Deblurring™, the scalp-recorded activity was mapped onto the cortical surface non-invasively. Even though there were limitations, uncertainty, and technical problems identified from the studies conducted, this thesis paves the way for future studies which investigate how the application of HR-EEG with Deblurring™ technique can be valuable for epilepsy surgery. Deblurred HR-EEG mapping may be able to improve the current pre-surgical evaluation for epilepsy patients by acting as the last non-invasive mapping effort before intensive ECoG monitoring.
BIBLIOGRAPHY


Au-Young SMW, Shen H, & Yang CR. (1999). Medial prefrontal cortical output neurons to the ventral tegmental area (VTA) and their responses to burst-patterned stimulation of the VTA: neuroanatomical and in vivo electrophysiological analyses. *Synapse*, 34, 245-255.


Dougherty RF, Au Young SMW, Giaschi DE, Bjornson BH, & Wong PKH (1998). Comparison of visual activation measured by fMRI and high resolution EEG. *Neuroimage*, 7(4II), S309.


APPENDIX 1

SEGMENTATION OF ANATOMIC MAGNETIC RESONANCE IMAGES

Segmentation is the process of assigning labels to pixels in 2-D images or voxels in 3-D images based on structure. The image is split up into segments, or regions, or areas. It is essential in medical imaging for quantification of outlined structures and for 3-D visualization of relevant image data. Segmentation is an important image processing step for:

- identifying anatomical areas of interest, e.g. landmarks and external markers, for diagnosis, treatment, or surgery planning paradigms
- preprocessing for multimodality image registration, and
- improved correlation of anatomical areas of interest with localized functional metrics

In this thesis, segmentation of each subject’s cortical surface is done to allow registration of the deblurred data and other functional mapping results on the cortical surface. The deblurred HR-EEG is superimposed on the “exposed” cortical surface, segmented from the subject’s MRI by a semi-automatic edge-based segmentation method available within the Manscan® Program (SAM Technology, San Francisco, CA, USA). Patients’ MRIs are also segmented by manual delineation to produce the cortical surface 3-D images with NIH Image (Bethesda, MD, USA) and VoxBlast software (Fairfield, IA, USA) to produce a more detailed brain cortical surface diagram. This is done for intra-operative correlation as well as for co-registration of grid data. Grid electrode positions are registered onto the segmented cortical surface by comparing the anatomical structures between the operative photos and the segmented brain.
APPENDIX 2

DATA OF STUDY A-2 (MAPPING OF THE PRIMARY SOMATOSENSORY CORTEX BY ELECTRICAL STIMULATION)

Table A1  Study A-2: Scalp Data - Left Index Finger Stimulation

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>PEAK ELECTRODE</th>
<th>MAX AMPLITUDE (µV)</th>
<th>SCALP AREA (cm²)</th>
<th>ADJUSTED SCALP AREA (divided by 1.58) (cm²)</th>
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Standard Deviation: 6.68
Variance: 44.6

Table A2  Study A-2: Scalp Data - Right Index Finger Stimulation

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Average: 17.53
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### Table A3  Study A-2: Deblurred Data - Left Index Finger Stimulation

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### Table A4  Study A-2: Deblurred Data - Right Index Finger Stimulation

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