Reorganisation of Sensorimotor Function in Children with Brain Disease

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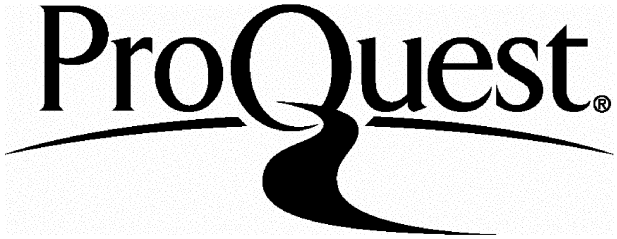

Abstract

Introduction: In this study, paradigms were developed for the investigation of sensorimotor function in children using functional MRI (fMRI), somatosensory evoked potential (SEP) recordings and behavioural measures. These techniques were applied both to normal controls subjects and to children with brain disease. A major aim was to investigate the remarkable recovery of function that can take place following brain injury sustained early in life.

Methods: Three fMRI paradigms were developed, namely active movement of the hand, passive flexion/extension movement of the fingers and median nerve stimulation. In addition, SEPs of functional cortical responses to stimulation of the median nerve were recorded at high temporal resolution. Finally, the extent of residual or recovered sensory and motor hand function was assessed using behavioural tests, including grip strength and double simultaneous stimulation. In one set of investigations, all three techniques were applied to children following hemispherectomy or children following vascular damage to the middle cerebral artery territory, to examine the pattern of residual sensorimotor function following brain injury. In a second study, fMRI was carried out in pre-surgical paediatric patients for mapping of the sensorimotor cortex in preparation for surgical resection of lesions in the vicinity of this cortical region.

Results and Discussion: fMRI was successful in locating the hand cortical sensorimotor area in 11 out of 12 paediatric patients pre-operatively, and was of value to the neurosurgeon in helping to delineate the boundaries of subsequent cortical resection. In patients following stroke and hemispherectomy, a combination of fMRI, SEP and behavioural techniques provided evidence for inter-hemispheric reorganisation of sensorimotor function through ipsilateral sensorimotor pathways, and also suggested an increase in the involvement of ipsilateral secondary sensorimotor areas. The data also indicate that cortical sensorimotor reorganisation and functional recovery can be seen in patient both with congenital disease and with late-onset acquired disease, suggesting that factors additional to age at injury may influence the degree of residual function resulting from cerebral reorganisation.

Informed consent was obtained for all patients and controls, and the study was approved by the Great Ormond Street Hospital for Children/Institute of Child Health Research Ethics Committee.

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Chapter 1: General Introduction

1.1 Introduction

The purpose of the work described in this thesis is to examine the cortical representation of hand sensorimotor function in children who have suffered brain damage affecting the somatosensory or motor system. In particular, a primary aim of this study is to investigate the role of functional reorganisation in mediating sensorimotor recovery after brain damage. To this end, investigations have been performed using functional MRI (fMRI), somatosensory evoked potentials (SEPs), and behavioural measures, in three groups of patients: namely, patients who have undergone hemispherectomy, patients who have suffered a stroke, and patients who were candidates for resective surgery in the region of the sensorimotor areas.

This introductory chapter presents an overview of the literature on the somatosensory and motor systems in animals and man. Particular attention is given to the primary cortical representation of somatosensory and motor function and the pathways that connect these primary central areas to the peripheral systems. In Sections 1.3 and 1.4, the motor and somatosensory systems are discussed separately, although, as is evidenced by the literature review, the inter-dependence of these systems is well established. Emphasis is placed on the upper limb organisation (especially the hand), with a mention of other body parts only where appropriate. In Section 1.5, a review of brain plasticity and the mechanisms of reorganisation of somatosensory and motor function is provided. Section 1.6 details the aims of the research described in this thesis.

1.2 The sensory and motor systems - brief historical background

Partly due to an overreaction to the concept of phrenology, scientific opinion in the mid-1800s held that the entire cerebral cortex functions as one indivisible unit. Then in the late 1860s to early 1870s, Hughlings Jackson examined a number of patients with focal motor seizures and proposed that motor functions might be localised to particular areas of the cortex (Jackson, 1870; 1873). At the same time, several groups were investigating the cortex in animals and man, and discovered that discrete regions of the brain control movement in contralateral body parts (for example Friesch & Hitzig, 1870; Ferrier, 1873). In 1909, Brodmann put forward a system of nomenclature whereby

numbers are assigned to different regions of the cerebral cortex based on microscopic patterns of nerve cell bodies (cytoarchitectonics) (Brodmann, 1909). These areas were found to correspond with patterns of connections and separable brain functions (Figure 1.1). Several further studies found that motor effects are elicited most readily, and with the lowest stimulation intensities, from the pre-central gyrus (Grunebaum & Sherrington, 1903; Campbell, 1905; Leyton & Sherrington, 1917). This region is now referred to as the primary motor cortex, corresponding to Brodmann's area 4.

The 'sensory cortex' was first identified by Dusser de Barenne (1916). He showed that application of strychnine to a small area of the monkey's postcentral gyrus resulted in scratching of the skin in a particular area. He was thus able to use this technique to map the sensory cortex of the monkey. Much of our present-day understanding of the organisation of the somatosensory cortex stems from evoked potential studies in animal models, first described by Woolsey et al. (1942). They discovered that the post-central cortex was activated by tactile somatic stimuli (Brodmann's areas 1,2, 3a and 3b) (Figure 1.1). These areas were driven almost exclusively from the contralateral side of the body (similar in organisation to the motor system pathway). Although it is now almost universally accepted that the motor cortex is within the pre-central gyrus and the sensory cortex in the post-central gyrus, this is to some degree simplistic since there is much evidence to show an overlap in the anatomical pathways and functions of these two cortical areas (Uematsu et al. 1992a&b; Nii et al. 1996; for review see Canedo, 1997).

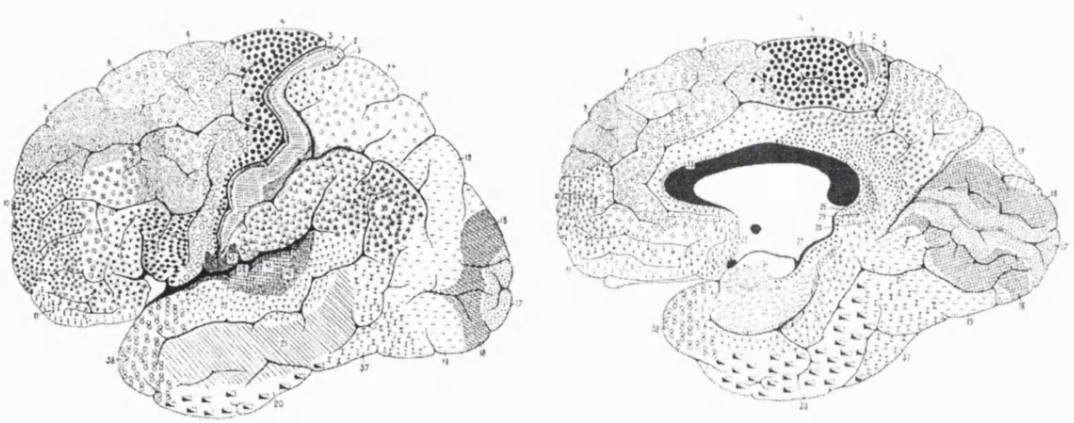


Figure 1.1: Cytoarchitectual mapping of the lateral and medial surface of the human cerebral hemisphere according to Brodmann (1909).

1.3 The motor system

The motor system can be divided into three major anatomical sections: the primary and associated motor cortical areas, the subcortical motor structures and the pathways from the brain to the muscles. Although these sections are described individually below, it is important to remember that in practice they generally act in unison to complete a functional motor cortex output. It is now accepted that there is a hierarchical organisation within the motor system, first recognised by Jackson (1873). Jackson argued that the most automatic responses are organised at the level of the spinal cord, whereas more complicated motor behaviours are organised by successively higher centres. This hypothesis has been supported by much work subsequently, indicating that the motor system consists of separate neural circuits that are linked, namely the spinal cord, the brainstem and reticular formation, the motor cortex and associated cortical areas.

1.3.1 The primary motor cortex

As mentioned previously, the primary motor area is identified as the region of the brain with the lowest threshold for eliciting motor responses on electrical stimulation. This area in the frontal lobe (Brodmann's area 4) occupies the precentral gyrus on the medial (paracentral) and lateral aspects of the cerebral hemisphere. The motor area is thicker (4.5 mm) than cortex elsewhere, and is classified as agranular heterotypical cortex because it contains a large number of pyramidal (Betz) cells, a feature unique to the motor area (Betz, 1874). These giant neurones are almost always situated in layer 5 which can obscure the basic six-layer pattern of the neocortex (Coulter et al. 1976; Murray & Coulter, 1981; Toyoshima & Sakai, 1982).

Since its discovery, the primary motor area has been thought to be involved purely in the execution of movement (Roland et al. 1980; Colebatch et al. 1991; Grafton et al. 1992b; Jenkins et al. 1997). Several recent reports, however, have suggested a more complex role of the primary motor area in generating movement. It is thought to play a decisive role in the co-ordination of movement and posture. This is possible because it has access, both directly and indirectly through collaterals, to structures governing the eye, head, trunk, and limb musculature. Changes have also been found to occur in the primary motor cortex in man relating to the learning and processing of complex sequences, mental rotation, planning muscle activity and movement preparation (for example Kawashima et al. 1994; Hoffman & Strick, 1995; Karni et al. 1995; Classen et

al. 1998b), which were processes previously thought to be controlled by associated motor areas. The precise role and functional organisation of this area is still under investigation and is further reviewed in Section 2.3.1.1 of Chapter 2, which describes cortical plasticity following simple and complex movement tasks.

In order for inferences to be made regarding the reorganisation of the primary sensorimotor area following brain damage, firstly an understanding is required of the location of the primary motor cortex in the normal human brain. The following three sections concentrate on the representation of the body, and in particular the hand, in the primary motor cortex. Firstly a brief overview is given of how the body is represented in the motor cortex, followed by a section detailing the localisation of hand motor function. Finally, a brief review of several hypotheses is given for how the primary motor cortex represents muscles or movements.

1.3.1.1 Somatotopy within the primary motor cortex

The excitation of neurones in the motor area manifests itself primarily in the movement of the contralateral musculature of the body. A somatotopic representation of the primary motor cortex was first demonstrated using electrical stimulation in patients by Penfield & Boldrey (1937). Subsequently, a more detailed illustration of the motor and sensory 'homunculus' (meaning 'little man', a map of the human cortical representation, relating to actual brain areas identified at surgery) was drawn either side of the central sulcus by Penfield & Rasmussen (1950) (see Figure 1.2 for the motor homunculus). These studies illustrated two important principles; firstly, the body representation in humans is arranged in an orderly fashion within the precentral gyrus, and secondly, the muscle groups used in movements that require fine control (for example in facial expressions and the hands) are given disproportionately large representation (see below). This ordered mapping of the body surface on to central neural structures is called 'somatotopy'. However, there is still debate as to the accuracy of this reported organisation (for review see Woolsey et al. 1979). Despite the popularity of this pictorial view of sensory and motor cortical representation shown in Figure 1.2, many scientists have criticised Penfield's method and naïveté (for example Schott, 1993). Many studies have demonstrated much intersubject variability as well as plasticity in the diseased brain. In addition, cortical electrical stimulation and recent functional imaging techniques have shown the activation of neurones beneath the surface of the brain. None of these factors was considered by Penfield during his studies on brain-diseased patients

(although it must be noted that the later functional imaging studies were obviously not available to him).

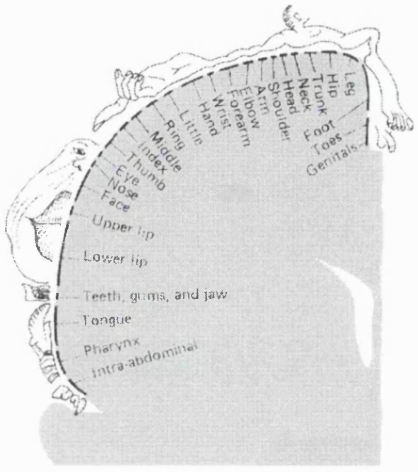


Figure 1.2: Map depicting the different body parts represented in the motor cortex, reproduced from (Penfield & Boldrey, 1937). The large portions of the motor area assigned to parts of the body in which movements are delicate and precise, reflect the many cortical neurones required for such movements.

For the human primary motor cortex (M1) in particular, positron emission tomography (PET) imaging has proved to be a useful technique capable of demonstrating some of the characteristics of somatotopy in the cortex (Colebatch et al. 1991; Grafton et al. 1991; 1993). Other techniques for examining somatotopy of the motor cortex include magnetoenchephalography (MEG) (Cheyne et al. 1991), scalp-recorded evoked potentials (Bischert & Deecke, 1986) and transcranial magnetic stimulation (TMS) (Cohen & Hallett, 1988; Wassermann et al. 1992). Many of these studies have also suggested an overlapping of within-limb functional areas, and many do not completely agree with the classical homunculus. These observations have been corroborated by more recent fMRI studies reporting separate but overlapping representations of individual fingers, elbow and toe movements in individual human subjects (Rao et al. 1995; Kleinschmidt et al. 1997). One explanation for the merging of functional activation sites for different movements could be that there is an overlap of muscle groups required to carry out the tasks (for review see Schieber, 1990). In fact, while the 'cartoons' depicting the M1 homunculus derived from electrostimulation studies feature somatotopic organisation even within the hand area, this is less clear from the original reports (Foerster, 1936; Penfield & Rasmussen, 1950).

1.3.1.2 Anatomical location of the motor hand area

Numerous studies have identified the location of the hand motor and sensory area in a specific segment of the pre- and postcentral gyrus (for example Penfield & Boldrey, 1937). This motor hand area has a characteristic shape: it is knob-like, most often having the form of an inverted omega, a 'bayonet-shaped' hook or a horizontal epsilon when examined in the axial plane, and it appears as a posteriorly directed hook when viewed in the sagittal plane (Salamon et al. 1991; Talairach & Tournoux, 1993; Yousry et al. 1997). It has been nicknamed the precentral 'knob' or 'hook' or 'knuckle' by many neuroscientists (Naidich & Brightbill, 1995; Yousry et al. 1997). The knob projects to the middle genu of the central sulcus, the middle being the posterior convex in contrast to the superior and inferior genu that are anteriorly convex (first described by Testut, 1911). It has also been identified as the 'upper genu', in contrast to the inferior genu which corresponds to the projection area of the face over the external aspect of the hemisphere (Rumeau et al. 1994). The pre-central knob can be regarded either as an 'insulization' (Salamon et al. 1991), or as a protrusion of the precentral gyrus towards the central sulcus (Yousry et al. 1997). This knob can also be located on the cortical surface by the neurosurgeon; however its configuration is less characteristic than it is at deeper levels. It appears as the structure opposite to the intersection of the superior frontal gyrus with the precentral sulcus (Kido et al. 1980; Yousry et al. 1997). The identification of such a landmark clearly increases the accuracy of locating the precentral gyrus. Other landmarks for locating the precentral gyrus have also been adopted, such as the anterior ascending and horizontal rami of the sylvian fissure (Ebeling et al. 1989; Naidich et al. 1995) and the ramus marginalis of the cingulate gyrus (Naidich & Brightbill, 1995). However, with all methods large inter-rater variability exists (Sobel et al. 1993).

1.3.1.3 Are individual muscles or movements represented differently in the primary motor cortex?

The discovery of a somatotopic map raised a new question of whether local areas in the motor cortex represent individual muscles or rather elementary movements involving the co-ordinated activity of several muscles. Many studies have been carried out in an attempt to answer this question, but there have been conflicting findings (for a review see Schieber, 1990). In humans, lesions to the motor cortex or corticospinal tract typically result in a profound and lasting deficit in the ability to individuate finger

movements, despite retaining the ability to flex and extend all the fingers together (Twitchell, 1951; Penfield & Jasper, 1954). On the basis of these studies and of animal studies (Passingham et al. 1983), the motor cortex appears to be necessary for individuation, but how does it impart this ability?

Using cortical stimulation in monkeys, apes and humans, mapping evidence has accumulated to demonstrate cortical representation of individual muscles (Penfield & Boldrey, 1937; Woolsey et al. 1979; Cheney & Fetz, 1985). There has been growing evidence, however, to suggest that although the dominant projection from a local area of cortex may be to a single distal muscle, a single output neurone in the cortex often has many collaterals that may influence several muscles, for example within the hand (Fetz, Cheney, 1980; Cheney et al. 1985; Buys et al. 1986; for review see Lemon, 1988). In addition, the cortical regions representing different muscles appears to overlap extensively (Strick, 1988; Nudo et al. 1992; Schieber & Hibbard, 1993; Sanes et al. 1995; Volkmann et al. 1998; Hlustik et al. 1999). It appears likely that there is a convergence from different cortical points on to a single pool of motor neurones, not a direct one-to-one relationship, which may be irrespective of a detailed somatotopic relationship. Accordingly, it is possible that a single finger can be activated from different locations in the motor cortex, depending upon the complex patterns of movement in which it is involved (Donoghue et al. 1992). Furthermore, Galea & Darian-Smith (1994), and subsequently Kawashima et al. (1994) and Geyer et al. (1996), proposed that rather than one homunculus in the primary motor cortex in man there may be two or three, so for example finger movements can indeed be obtained by stimulating several areas of the motor strip.

It has also been suggested that the motor cortex is specialised not only for individual muscle movements represented somatotopically but in addition discrete finger, hand and arm movements (Humphrey, 1986; Schieber, 1995; Kleinschmidt et al. 1997). For example, the thumb may move alone, in conjunction with the index finger, or with the whole hand as in a grasp. All of these actions involve the thumb motor cortex region, but various non-thumb movements (such as joint stabilising) must also occur to complete each of the tasks listed. Rao et al. (1995) and Sanes et al. (1995), using fMRI, both found that a large expanse of the human precentral gyrus exhibits activation during individuated finger and wrist movements, and suggested that the neurones in this area form a distributed and co-operated network that can simultaneously and optimally control collections of arm muscles. More specifically, Schieber (1995) reported that for 'movements of different fingers, a given muscle could act as an agonist, antagonist, or stabiliser of the digit it serves'. So movements must involve a large portion of the motor

cortex, beyond just the area of a single digit. There are, however, problems with this view. Firstly, cortical stimulation of the hand area may produce isolated movement of the thumb, but an isolated movement of any other digit is evoked only rarely (Penfield & Boldrey, 1937; Woolsey et al. 1952; 1979). Secondly, these studies showed extensive overlapping of the regions for each finger. In addition, if movements of the different fingers were represented in a lateromedial somatotopy (as depicted by Penfield & Rasmussen, 1950), one might expect occasionally to see human patients who have cortical lesions with impaired thumb movements but not movements of the little finger, or vice versa. No such cases have been reported to date.

Another view is that the entire hand cortical area participates in producing a discrete movement of any given finger. An integrated mosaic of efferent neurones within the motor cortex hand area may project to particular muscles (Asanuma & Rosen, 1972; Gould et al. 1986). There is evidence from a number of different studies in support of this model of the organisation of the primary motor cortex (Humphrey, 1986; Fetz, Cheney, 1987; Lemon et al. 1987). Schieber & Hibbard (1993) conjectured that rather than being specified by a somatotopic map, each finger movement appears to be specified by a neuronal population distributed throughout the motor cortex hand area. The model would be consistent with the failure of cortical lesions to impair isolated digits, and would also be consistent with the difficulty in evoking discrete movements of single fingers in cortical stimulation studies and with the extensive overlapping functional cortical areas and diverging muscular projections of the cortico-motorneuronal cells.

There has been no definitive evidence as yet to exclude any of these hypotheses or even to suggest the likelihood of one being prominent over any of the others. Many groups hypothesise that the various ideas mentioned above should not be considered mutually exclusive, as each may pertain to particular movements of particular digits and/or the degree of mechanical independence of the digits involved.

1.3.2 Association cortical areas of the motor system

Other cortical areas have been shown to be linked to the primary motor cortex, so comprising a large neural circuit within the brain and contributing substantially to motor functional outputs. These are the supplementary motor area (SMA), situated on the medial portion of the superior frontal gyrus (Brodmann's area 6), the premotor area, found on the lateral surface of the frontal gyrus (also Brodmann's area 6), the

postcentral somatosensory area (Brodmann's areas 1, 2, 3, 5, and 7), and the second somatosensory cortex (S-II) (area 43). However the anatomical boundaries, and even the nomenclature, of these structures are not precisely defined (for review see Donoghue & Sanes, 1994). All of these areas are thought to contribute directly to the fibres of the descending pyramidal system (Murray & Coulter, 1981; Martino & Strick, 1987; Hutchins et al. 1988; Dum & Strick, 1991). It has been discovered that these and other components of the motor system (such as the subcortical areas and within the spinal cord) contain individual somatotopic maps (Muakkassa & Strick, 1979; Hutchins et al. 1988; Dum & Strick, 1991; Lim et al. 1994). The SMA and premotor area receive projections from many other cortical areas, including the parietal lobe, thalamus, cerebellum, basal ganglia, sensory and visual areas (among others, Matelli et al. 1986; Wiesendanger, 1986; Hutchins et al. 1988; Mushiake et al. 1991). However, each has different projections from some or all of these structures, indicating that they all have unique functions in the final specification of movement.

Approximately 20% of corticospinal fibres have been found to originate from the primary somatosensory cortex (S-I) postcentrally (Brodmann's areas 3a, 3b, 2, and 1), S-II (area 43) and the posterior parietal cortex (areas 5 and 7) and project to the dorsal horn (Jane et al. 1967; Coulter et al. 1976; Kuypers, 1981; Porter & Lemon, 1993). This is in line with cytoarchitectonic evidence that pyramidal cells can be found in the post- as well as precentral gyrus (Brodmann, 1909; Soso & Fetz, 1980; Jennings et al. 1983). The postcentral gyrus thus contributes to the formation of the pyramidal tract and may therefore be additionally activated by the efferent part of the motor task. Similarly, sensory responses can be elicited by stimulating the motor area (for example Powell & Mountcastle, 1959). In addition, the role of the left parietal cortex has been shown to be associated with motor attention (Rushworth et al. 1997). Due to the apparent overlapping functions and projection systems between the primary sensory and motor cortex they are usually considered as an integrated region of 'sensorimotor cortex' surrounding the central sulcus.

In brief, the SMA is generally thought to play an important role in the programming of internally remembered complex sequences of movement (Roland et al. 1980; Passingham, 1987; Jenkins et al. 1994; Catalan et al. 1998), and also in the preparation of movement and in motor planning (Fox et al. 1985; Grafton et al. 1992a; Rao et al. 1993; Richter et al. 1997). The premotor cortex is thought to be involved in 'externally generated' movement (see for example Passingham, 1989; 1993; Jenkins et al. 1994; Sadato et al. 1996a; Catalan et al. 1998). However, the literature demonstrates that the precise role of these two motor association areas is not yet clear. They appear to have

multiple roles in the control and production of movements, possibly explaining the huge contradictions in the literature (for review see Passingham, 1993; 1996; Tanji & Shima, 1996).

Additional motor areas have also been identified on the medial and lateral cortical surface (for example Luppino et al. 1991; Shima et al. 1991; Vogt et al. 1992). These are the anterior cingulate gyrus (Grafton et al. 1993), the frontal eye fields (Mann et al. 1988), and pre-frontal cortex (di Pellegrino & Wise, 1991; di Pellegrino & Wise, 1993; Jenkins et al. 1994).

1.3.3 Subcortical motor structures and pathways

Fibres of the pyramidal system give off collateral branches as they traverse the internal capsule and brain stem. These branches terminate in a number of subcortical structures, namely the corpus striatum of the basal ganglia, red nucleus, pontine nuclei, inferior olivary nucleus, cerebellum and the reticular formation (Phillips & Porter, 1977). Perhaps the most researched of these subcortical structures are the cerebellum and the basal ganglia. It is thought that the cerebellum acts as a 'comparator', to adjust the actions of both the brain stem motor structures and the motor cortex (for example Parsons et al. 1997; Jueptner & Weiller, 1998). It receives and compares descending control signals responsible for the intended motor response (i.e. its planning and execution) with sensory signals resulting from the consequences of ongoing motor actions (Jueptner et al. 1996; Xue et al. 1997). The output of the cerebellum is delivered both to the periphery and back to the cerebral cortex (particularly the primary motor and premotor areas (Schell & Strick, 1984)), so that any discrepancies between the intended and actual motor actions can be corrected. The cerebellum is also thought to have a direct involvement in motor execution (Shibasaki et al. 1993), co-ordination of movement (Llinas & Welsh, 1993), initiation and execution of planned movement (Krams et al. 1998), motor learning (Friston et al. 1992; Jenkins et al. 1994; Sadato et al. 1996a), and sensory processing (Fox et al. 1985). The connections of the cerebellum are ordered such that each cerebellar hemisphere is concerned with ipsilateral muscles; however it is also thought to have a role in the control of bilateral limb movements (Ellermann et al. 1993; Fox et al. 1985).

The basal ganglia consists of the corpus striatum (subdivided into the caudate, putamen and globus pallidus, the latter two areas collectively termed the lentiform nucleus), subthalamic nucleus and substantia nigra. The putamen is the main sensorimotor

territory (Lehericy et al. 1999) and is the focus of the majority of inputs into the basal ganglia from the primary motor and sensory areas, premotor and supplementary motor cortices (Alexander & Crutcher, 1990). Some of the roles that have been postulated for the function of the basal ganglia are the selection, control and preparation of specific motor programs, starting and practising of sequential actions, inhibition of unwanted movements and the promotion of motor learning and planning (Brooks, 1995; Bucher et al. 1995; Boecker et al. 1998; Krams et al. 1998). Bilateral activation in the basal ganglia may occur with unilateral motor tasks; however it was more significant on the contralateral side (Hallett, 1993). The involvement of the cerebellum and basal ganglia in motor action and other functions is still very much undetermined (for reviews see Leiner et al. 1993; Brown & Marsden, 1998; Jueptner & Weiller, 1998).

1.3.4 The motor pathway from brain to muscle

The simplest functional structure in the motor hierarchy is the spinal cord. It is responsible for organising the most automatic and stereotyped responses to stimuli in addition to transmitting signals from higher cortical areas to carry out more skilful motor outputs. Two pathways run within the cord, the corticospinal tract (or so-called pyramidal tract as it mainly traverses the pyramid of the medulla and terminates in the spinal cord), and the corticobulbar tract (which has the same relationship to motor neurones of the cranial nerves as the corticospinal tract to motor neurones of the spinal cord). Both tracts come under the heading of the pyramidal motor system. In this section, and for the purpose of this thesis, emphasis will be on the organisation of the corticospinal tract in the transmission of motor information.

The corticospinal tract comprises of motor neurones within the spinal cord, and is the major cortically-derived descending pathway (see Figure 1.3 for overview; Canedo, 1997). A large portion of cortical neuronal fibres forming the origin of the tract are from the primary motor area. In the cat and monkey, this area contributes more fibres to the corticospinal tract than any other region (Porter & Lemon, 1993), ranging from 31% (Russell & DeMyer, 1961) to 51% (Toyoshima & Sakai, 1982). In the human, approximately 40-80% of the pyramidal fibres originate in the precentral gyrus (Jane et al. 1967; Kuypers & Brinkman, 1970; Kuypers, 1981). The remainder of the fibres in the corticospinal pathway are projection fibres arising from association areas within the frontal and parietal lobes (see Section 1.3.2).

The corticospinal tract exists in most mammals, but it reaches its largest size and importance in humans where much of its function deals with voluntary control of the upper and lower limbs, in addition to modifying sensory impulses to regulate ascending information (Armand, 1984). The tract allows the motor cortex to play a crucial role in the co-ordination of movement and posture via direct and collateral branches to structures governing eye, head, neck, trunk and limb musculature (Canedo, 1997). No other neurones in the brain besides the pyramidal tract cells have such wide access to other structures within the central nervous system. The following description of the motor pathway applies mainly to humans; however, in principle this pathway is similar in most higher and lower primates.

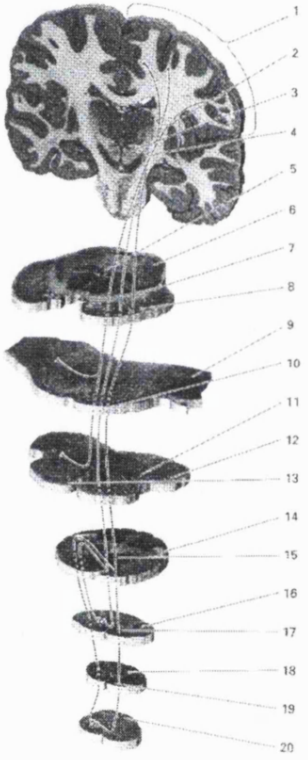


Figure 1.3: The contralateral pyramidal motor system (taken from Barr & Kiernan, 1993). Refer to text for description. Structures labelled of particular interest are the motor cortex (1), the internal capsule (4), the cerebral peduncle (8), the pons (10), the ventral horn of the spinal cord (17) and the ventral corticospinal tract decussating in the spinal cord (19). The lateral corticospinal tract is seen to decussate at the level of the pyramids (13). The ipsilateral corticospinal pathway is not indicated on this diagram.

The tract emanates from the cortical areas mentioned above, traversing the corona radiata and narrowing down to enter the posterior limb of the internal capsule (running between the lentiform nucleus and thalamus). There is a discrete somatotopic organisation in the internal capsule, as with all areas of the motor system. Fibres arising from the medial frontal lobe (for example from the SMA) pass through the anterior limb, those arising

from the premotor cortex descend through the genu and anterior portion of the posterior part of the internal capsule, and finally those fibres originating from the primary motor cortex itself pass through the middle third of the posterior limb of the internal capsule (Fries et al. 1993). The descending pathway gives off branches to the ventral lateral and centre median areas of the thalamus (Parent & Hazrati, 1995). The tract then continues through the middle three-fifths of the basis pedunculi within the midbrain and is broken up into many fasiculi (individual neuronal tracts) by clusters of pontine cells as it crosses to the ventral portion of the pons. The fasiculi coalesce in the 'pyramids' on the anterior surface of the medulla to form the descending compact corticospinal tract. In general it is taken that, within the brainstem, fibres for the upper part of the body tend to be medial and those for the lower half lateral, although this is known to lack precision because of the intermingling of fibres concerned with different parts of the body.

In 1981, Kuypers noted in primates that the descending pathways could be divided into two major groups according to the location of their terminations in the spinal cord, and this corresponded to a systematic difference in their functional roles (Kuypers, 1981). One group is located in the medial part of the ventral horn (in the anterior funiculus of the spinal cord) and the other much larger group lies more laterally (in the lateral funiculus of the spinal cord) (Kuypers, 1981). The latter group, which largely crosses the midline at the caudal level of the medulla, constitutes the 'lateral corticospinal tract' (described below). The group within the ventral horn is called the 'ventral corticospinal tract', most of the fibres of which do not decussate until they reach the spinal cord. These two corticospinal tracts were also subsequently delineated in humans (Nathan et al. 1990). The two motor neurone groups connect to different muscles; the lateral group project to distal muscles such as those of the digits, and those innervating the axial muscles lie in the medial part of the ventral horn (Ghez, 1991). In this section, concentration is placed on the lateral corticospinal tract; the ventral corticospinal tract is further mentioned only in Section 1.3.4.1.

It is at the caudal end of the medulla (at its junction with the spinal cord) where a large number of the corticospinal fibres cross the midline, in what is known as the 'decussation of the pyramids', to form the lateral corticospinal tract. The portion of crossing fibres in the medulla is approximately 75% to 85%, although it varies between individuals (for review see Nyberg-Hansen & Rinvik, 1963). The decussation consists of coarse bundles, with a portion of the fibres from pyramids on both sides of the medulla crossing the midline. Once the fibres have crossed over, the axons regroup to form direct pathways projecting down to the spinal cord grey matter. Because of this regrouping, the corticospinal tract is sometimes referred to as the pyramidal tract. This

usage is incorrect, however, as some fibres leave the medullary pyramids to terminate in brain stem nuclei such as the dorsal column nuclei. Within the spinal cord, such descending corticospinal fibres lie in the dorsal part of the lateral white column of the spinal cord and appear to be represented by longitudinal columns of motorneurons that innervate a given muscle (Romanes, 1951; Sterling & Kuypers, 1967). Davidoff (1990) suggested that the lateral corticospinal tract may vary considerably in size from person to person.

The lateral corticospinal tract descends within the spinal cord, giving off many collaterals, with only between 5% and 20% synapsing directly with motor cells (Kuypers, 1981; Donoghue & Sanes, 1994; Canedo, 1997), most synapsing with intercalating neurones which in turn synapse with alpha motor neurones and some gamma motor neurones (Preston & Whitlock, 1961). This presence of direct connections from the cortex to the motor neurones allows the ability to control individual muscles or movements independently from one another. This important function is termed the 'fractionation of movement' (Phillips & Porter, 1977; Porter, 1985). Further evidence for this control of movement comes from several investigations in monkeys. In the study, it was shown that the animals' development into making fine finger movements over the first 7-8 months parallels the development of the corticomotorneuronal connections (Lawrence & Hopkins, 1976). In two subsequent studies, corticomotorneuronal cells showed a greater increase in activity when monkeys performed a precision grip as opposed to the less fractionated movement of a power grip (Muir & Lemon, 1983; Buys et al. 1986). In addition, sectioning of the corticospinal tract or ablation of the motor cortex always results in deficits of fine finger movement in animals (Lawrence & Kuypers, 1968a; Hepp-Reymond et al. 1974; Passingham et al. 1983) and man (Penfield & Jasper, 1954; LaPlane et al. 1977). Although a patient or animal with such a lesion may retain the ability to flex and extend all the fingers together, the ability to move fingers individually remains permanently deficient. For a more detailed review of the cortical representation of movements see Section 1.3.1.3.

Although most of the corticospinal fibres decussate in the lower medulla to form the contralateral lateral corticospinal tract, 25% remain uncrossed (Nyberg-Hansen & Rinvik, 1963; Yakovlev & Rakic, 1966; Brodal, 1981; Davidoff, 1990). The origin and termination of these descending ipsilateral fibres are described in detail below (Section 1.3.4.1).

In addition to the direct projection of the corticospinal pathways to the spinal motor system, there is also an indirect influence via corticospinal connections with various

parts of the brain stem. The most well understood are the vestibulospinal (originating in the lateral vestibular nucleus) and the reticulospinal (originating in the reticular formation) tracts, which are largely concerned with postural adjustments of movement and balance (Kuypers, 1981; Holstege, 1996). In addition, cortical fibres are also thought to maintain indirect connections with the spinal cord via terminations within the superior collicus and tegmentum. These connections are important in co-ordinating head and eye movements. All of these tracts have ipsilateral projections and are also described in Section 1.3.4.1. Although to date most information about these tracts has been derived from research in animals, it seems probable that the reticulospinal tracts mediate control over most movements that do not require manual dexterity or the maintenance of balance, and the vestibulospinal pathway appears to be essential for highly skilled accomplishments of motor co-ordination, such as that required in a gymnast.

1.3.4.1 The ipsilateral corticospinal pathway in the normal individual

There has been much debate over the last few decades as to the origin of ipsilateral sensorimotor responses to unilateral movements (Roland et al. 1980; Kim et al. 1993a&b; Salmelin et al. 1995). On the basis of anatomical data and mapping techniques, evidence has been collected for the presence of ipsilateral sensory and motor pathways in the normal central nervous system that may account for these responses (for example Nakahama, 1958; Korvenoja et al. 1995; Noachtar et al. 1997). Several groups, however, argue for other afferent pathways mediating ipsilateral responses, such as transcallosal fibres, subcortical pathways, other cortical links such as through the second somatosensory cortex (S-II), or simply volume conduction of the potentials generated in the contralateral hemisphere (Larson et al. 1966; Williamson et al. 1970; Tamura, 1972; Aleev & Varezhkin, 1978; Kuksova & Sumskii, 1983; Kakigi, 1986). In this section, the normal anatomical ipsilateral pathway is summarised; its functional application in the diseased brain is described later in Section 1.3.

In addition to the contralateral lateral corticospinal tract described in Section 1.3.4 above, ipsilateral lateral and ventral corticospinal tracts have also been identified in the motor system of man (Nathan & Smith, 1955; Nathan et al. 1990; for review see Jones et al. 1989). The pathways have also been found in the monkey (Glees & Cole, 1952; Liu & Chambers, 1964; Semmes & Mishkin, 1965). Both tracts are smaller than the crossed lateral corticospinal tract. Of the 25% uncrossed fibres in man, it has been found that 15% are in the ventral ipsilateral corticospinal tract (Nyberg-Hansen & Rinvik, 1963), and the remaining 10% in the ipsilateral lateral corticospinal tract (Nyberg-

Hansen & Rinvik, 1963; Brodal, 1981; Toyoshima & Sakai, 1982). In contrast, however, Nathan & Smith (1973) suggested that the lateral corticospinal tract carries the majority of ipsilateral fibres. The various tracts mentioned are thought to terminate in different areas in the spinal cord. Several studies have reported that the majority of axons of the ipsilateral ventral tract decussate in the spinal cord and thus terminate contralaterally in the ventral horn to innervate the contralateral side (Figure 1.3) (Liu & Chambers, 1964). The remaining ventral tract axons, however, terminate predominantly in the ipsilateral ventral horn. In contrast, all of the ipsilateral lateral corticospinal tract remains uncrossed and terminates in the ipsilateral dorsal horn, ventral horn and intermediate zone (Glees & Cole, 1952; Liu & Chambers, 1964).

The cortical origin of these ipsilateral corticospinal fibres has been investigated (Liu & Chambers, 1964). It was demonstrated that both ipsilateral and contralateral lateral corticospinal tracts arose from the precentral area and part of the postcentral area. In contrast, the ipsilateral ventral tract was found to originate only from the precentral gyrus. The suggestion of ipsilateral tracts originating precentrally has recently been supported by Toro et al. (1994) and Wassermann et al. (1994), and also in fMRI studies demonstrating ipsilateral activation in the precentral area (for example Singh et al. 1998a). One study suggested that uncrossed corticospinal fibres terminating on spinal neurones controlling axial and proximal muscles originated mainly from area 6, anterior to the primary motor cortex (Weisendanger, 1981). Other studies have demonstrated a much wider cortical representation of ipsilateral motor projection fibres; however, the majority were found to arise from area 4 (Toyoshima & Sakai, 1982; Ghez, 1991; Ghez & Gordon, 1995). It was initially thought that ipsilateral descending projections only terminated on motor neurones innervating proximal limb muscles, as well as contributing to the bilateral cortical control of the axial musculature either directly through corticospinal pathways or indirectly via cortico-reticulospinal pathways (Liu & Chambers, 1964; Brinkman & Kuypers, 1973). Several studies have now shown ipsilateral cortical representation patterns in the precentral, premotor and SMA for distal parts of the upper limb (for example Tanji et al. 1988; Benecke et al. 1991; Wassermann et al. 1991; 1994). However these neurones formed only a small proportion of active neurones during hand movements. The results of these human studies suggest that ipsilateral projections from the primary motor cortex to the upper limb muscles exist but are considerably weaker than contralateral projections. The proximal muscles are mainly targeted, with distal muscles receiving only weak ipsilateral projections.

Certain brainstem pathways have also been found to contain a proportion of ipsilateral connections, in addition to contralateral connections. The lateral brainstem pathway

(predominantly the rubrospinal pathway) projects to the distal portion of the contralateral limb. The rubrospinal tract originates in the red nucleus and projects down to the dorsal part of the lateral column of the spinal cord. In contrast, the ventromedial brainstem pathways project bilaterally to axial and proximal muscles (Ghez, 1991). The ventromedial pathways consist of the vestibulospinal, reticulospinal and the tectospinal pathways (refer also to Section 1.3.4). In particular, the reticulospinal pathway originates predominantly in the premotor cortex (a small number of projections also arise from the primary motor cortex) which sends projections down to the reticular formation which in turn gives rise to a bilaterally organised reticulospinal tract (Lawrence & Kuypers, 1968b; Brodal, 1969; Benecke et al. 1991). This pathway is not thought to provide control of fractionated individual finger movements but does provide basic action patterns of the contralateral and ipsilateral trunk and the limbs.

The organisation of the descending motor pathways described above suggest that hemidecortication or focal sensorimotor lesions will have different consequences for distal and proximal movements. In principle, the spinal motorneurones innervating distal muscles contralateral to the side of the removed hemisphere will lose a considerable amount of input, whereas the control of proximal muscles is largely maintained through brainstem pathways and ipsilateral cortical connections both with the spinal cord and ventromedial brainstem systems. It follows that proximal muscles ipsilateral to the side of surgery or lesion may be only slightly affected but distal muscles may show a more pronounced deficit (for example Jones et al. 1989; Dijkerman, 1996).

1.3.5 Interhemispheric pathway - the role of the corpus callosum

An additional source of connections into and out of the motor system comes from the corpus callosum, which relays information from one hemisphere to another. Most regions of the sensory and motor cortex are directly connected between hemispheres, although it was originally thought that a major exception to this rule is the distal portion of the limbs. These regions (namely the hand and foot areas) were thought by many to be functionally disconnected from each other in older children and adults, and to act totally independently (for review see Ghez, 1985). However, recent evidence from clinical studies of patients with complete commissurotomies or agenesis of the corpus callosum has suggested that the corpus callosum may play a role in bimanual motor co-ordination and the pre-motor control of movement, and may also inhibit the opposite hemisphere from interfering when a simple unimanual movement is required (Geffen et al. 1994; Sauerwein & Lassonde, 1994; see Section 6.4.2 of Chapter 6). A number of

studies have demonstrated that uncrossed (unimanual) motor and sensory responses can be controlled by one hemisphere, whereas crossed (bimanual) responses require communication between the two hemispheres (such as Reynolds & Jeeves, 1977; Chiarello, 1980; Jeeves et al. 1988; Berlucchi et al. 1995). In the normal brain this communication is effected rapidly by the corpus callosum, whereas in the acallosal brain it must occur much more slowly by way of less efficient alternative interhemispheric pathways. In addition, histological evidence has accumulated for the anatomical connection of the primary, secondary and association portions of the sensory and motor areas of both hemispheres through the corpus callosum (Aboitiz, 1992). Plasticity within discrete sections of the corpus callosum related to functional demand has been demonstrated in adults (Schlaug et al. 1995). This supports the evidence of plastic changes of components of the structure during maturation in the first decade of life in humans (Huttenlocher, 1979).

1.4 The somatosensory system

1.4.1 The primary somatosensory area

The primary somatosensory area (area S-I) occupies the post-central gyrus on the lateral and medial (paracentral) surface of the cerebral hemisphere. It has been a focus of considerable research since the beginning of the century (Vogt & Vogt, 1919; Marshall et al. 1937). The post-central gyrus was designated to be the S-I area because it has the highest density of points that produce localised contralateral sensations (such as numbness and tingling) on electrical stimulation and during focal evoked potential studies (Marshall et al. 1941; Woolsey et al. 1942). Later, it was recognised to consist of four independent subdivisions according to Brodmann's cytoarchitectural map shown in Figure 1.1, namely areas 3a and 3b buried in the posterior bank of the central sulcus, and areas 1 and 2 on the surface of the postcentral gyrus (Merzenich et al. 1978; Kaas et al. 1979; Kaas, 1983) (Figure 1.4). Importantly, these different areas each contain distinct cortical representations of the body with different somatosensory receptors. Each of the four areas has its own pattern of extrinsic connections and most areas are reciprocally interconnected (see below). Recent reviews have tackled the debatable issue as to which of these four areas in the monkey S-I-complex should be considered the primary somatosensory cortex proper. Much evidence points to area 3b being the most likely of the primary S-I areas (for review, see Kaas, 1983).

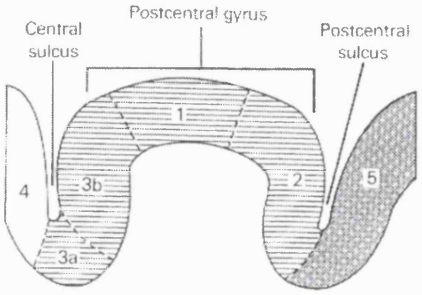


Figure 1.4: Organisation of the divisions of the primary somatosensory cortex, according to Kaas (1983).

As with the primary motor area, the primary somatosensory area represents the sensations of the body in an organised map or 'homunculus' over the cortex. The details of this map were determined by direct surface recordings of evoked potentials (Woolsey et al. 1942; 1979; Sutherling et al. 1992), the observation of sensations elicited by electrical stimulation of the cortex (Penfield & Boldrey, 1937) and more recently by functional imaging studies (Fox et al. 1987; Moore et al. 1996; Nakamura et al. 1998). The contralateral body portions of this map are laid out in a similar distribution to the motor area homunculus, with only a small number of modifications as to which structures are included and their representative size in the somatosensory cortex (see Figure 1.5). The size of the cortical area for a particular part of the body is determined by the functional importance of the part and its need for tactile sensitivity (in a similar way to the dependence of the motor map on functional muscle demand). Correspondingly, the size of the receptive field on the body surface varies in precise proportions (but inversely) with the size of the body surface represented in the cortical map. So, for example, the hands and lips have a large number of cutaneous receptors and receptive fields in a small location and so have the greatest cortical representation (Figure 1.5).

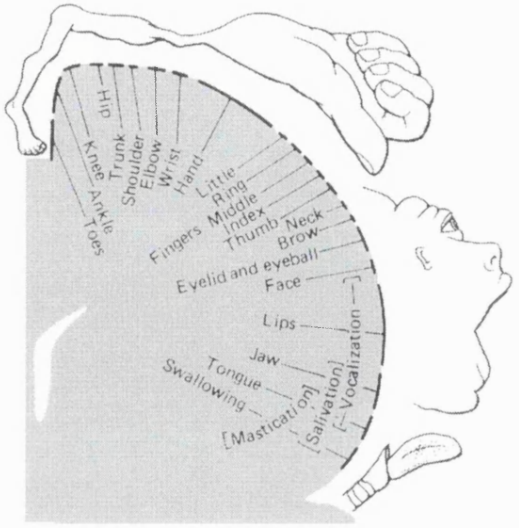


Figure 1.5: Representation of body parts in the primary somatosensory cortex (Penfield & Boldrey, 1937).

Advances in techniques to study brain function have provided alternative methods to confirm or challenge the somatosensory somatotopic homunculus depicted by Penfield & Boldrey (1937). For example, somatotopy has been examined in the primary sensory cortex with PET imaging in subjects receiving vibrotactile stimulation (for example Fox et al. 1987). One recent study with fMRI using tactile stimulation of the lips, fingers and toes localised representations on the post-central gyrus in accordance with Penfield's homunculus (Kapfer et al. 1999). Another recent fMRI study examined somatotopy in the primary sensory cortex using air puff stimuli applied to the ventral surface of the left arm (Servos et al. 1998). It was shown that two areas of the primary somatosensory cortex represented the human arm. One of these regions was located deep within the central sulcus and may correspond to area 3b, and the other region was more lateral and posterior and most likely corresponds to area 1.

Much work has been carried out to characterise the functions of the separate sub-divisions in the primary sensory cortex. For example, several studies of monkeys examined the effect of small lesions in the hand region of each of the sub-divisions 3a, 3b, 1, and 2 (Semmes & Turner, 1977; Carlson, 1981; Hikosaka et al. 1985). The results showed that lesions in area 3b produced deficits in the discrimination of texture, as well as the size and shape of objects. In contrast, lesions in area 1 produced a selective deficit in the ability to assess the texture of objects, whereas the ability to differentiate size and shape were altered and finger co-ordination impaired with lesions in area 2. This is consistent with the idea that area 3b (as well as 3a), located deep within the central sulcus, is the initial and principal target for the afferent projections from the

ventral posterior lateral nucleus of the thalamus. This area then projects to the somatosensory areas 1 and 2, dividing the functions of the somatosensory system between them (supported by Garraghty et al. 1990). A functional segregation between these areas was also suggested by Kaas et al. (1979, 1983) and Mountcastle (1984). Using microelectrode recordings, it was discovered that area 1 responds to the activation of rapidly adapting cutaneous receptors; area 3b responds primarily to the activation of rapidly or slowly adapting cutaneous receptors; area 3a responds to deep input from muscle stretch (and therefore is assumed to be concerned with the processing of proprioceptive information (Phillips et al. 1971; Jones & Porter, 1980) and sends axons to the corticospinal tract (Armand & Kuypers, 1980)); and finally cells in area 2 respond to deep non-cutaneous pressure. But additional submodalities exist within each region. It is clear from this description of the sensory cortex that there is an overlap in function between the sensory and motor cortices. In addition, it has been shown that sensory responses can be elicited from the motor area of the precentral gyrus as well as motor responses by stimulation of the primary somatosensory area, as described in Section 1.3.2 (Powell & Mountcastle, 1959; Lemon & Porter, 1976).

1.4.2 Association cortical areas of the somatosensory system

Several cortical regions (in addition to the primary motor area) are functionally and anatomically linked to the primary somatosensory cortex, which modulates the final interpretation of a sensory stimulus. The second somatosensory area (S-II), the posterior parietal cortex, the granular prefrontal cortex and the limbic areas function through serial projections from the primary sensory cortex to form a distributed network of cortical areas for the higher-order processing of somatosensory inputs (Mauguiere et al. 1997). These cortical areas are interconnected either through cortico-cortical connections or via the thalamic relay through the medial pulvinar nucleus (Jones & Powell, 1970; Mesulam, 1981; Baleydier & Mauguiere, 1987). Of these areas, the most well understood are the S-II area and the posterior parietal cortex, which are depicted in Figure 1.6.

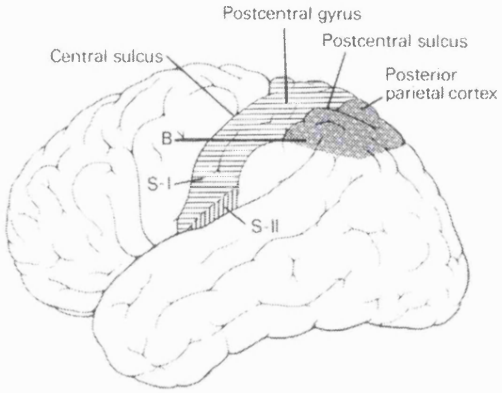


Figure 1.6: A lateral view of a cerebral hemisphere illustrating the approximate locations of S-I, S-II, and the posterior parietal cortex ('supplementary sensory area').

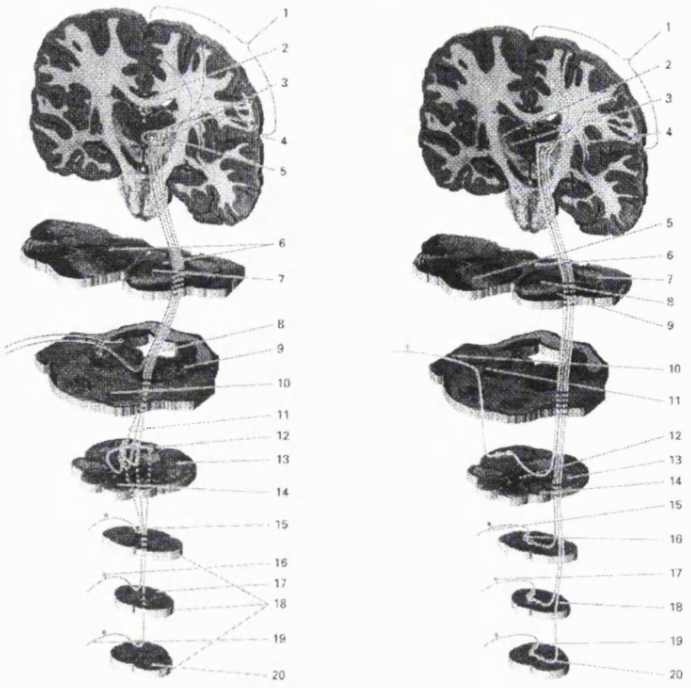
The S-II area is identified as a small region of cortex within the superior aspect of the sylvian (lateral) fissure, in accordance with the inferior region of the post-central gyrus known as the parietal operculum (Brodmann's area 43). It has been shown that between 40% and 90% of the neurones in S-II represents the receptive fields of body parts bilaterally in a somatotopic fashion as in S-I; the contralateral representation has been found to be predominant (Forss et al. 1994b; Hoshiyama et al. 1995; Kany & Treede, 1997; Simoes & Riitta, 1999). The functional role of this area is still under debate, but it is thought to be concerned with the discrimination of tactile inputs of texture and shape, tactile learning and memory (for example Hari et al. 1990; Burton et al. 1993; Ledberg et al. 1995), high frequency vibration (for example Fox et al. 1987), and the recognition and discrimination of pain (Coghill et al. 1994; Greenspan et al. 1999). The posterior parietal cortex lies on the lateral and medial surface of the parietal lobe, coinciding with Brodmann's areas 5 and 7. Its main afferent input is from the S-I area (Forss et al. 1994a; Mauguiere et al. 1997), and it is thought to be required for the identification and interpretation of tactile objects without visual aid. Damage to this area may also cause complex abnormalities in spatial orientation for the contralateral and ipsilateral halves of the body (Levine et al. 1978; Nixon et al. 1992; Richer et al. 1993).

1.4.3 The somatosensory pathway from touch to brain

For the purpose of this review and its relevance to the rest of the thesis, somatosensory pathways from the body to the cortex are described, pathways from the head largely being ignored.

The specificity of signals and their anatomical ascending pathway from the periphery to the cerebral cortex is determined by the somatic receptors involved and their afferent axons (for a review, see Turebjork et al. 1987; Hodge & Apkarian, 1990). According to this view, the distinctiveness of a sensation is predominantly based on stimulation of specific receptors and on the fact that specific sensory information travels along discrete neural pathways. In general, the brain makes use of temporal and spatial patterns of impulses from a large number of receptors of various types to form more complex tactile precepts such as the recognition of texture (Turebjork et al. 1987). Adams & Victor (1989) went on to suggest that many receptor types are not as specific as once thought, but that each responds preferentially (i.e. each has a lower threshold) to one form of stimulation in distinction to another. The sense of touch is caused by mechanical stimuli of the body via a number of types of cutaneous mechanoreceptor such as Pacinian corpuscles, Meissner's corpuscles (both of these are rapidly adapting mechanoreceptors, responding to pressure and velocity), Merkel cells, and Ruffini endings (slowly adapting receptors, which produce a sustained discharge with pressure and when the skin is held in a new position) (Iggo & Ramsey, 1974; Mountcastle, 1980). Proprioception, the perception of the position of the limbs and the sense of movement, is also signalled by specific receptors. The deep receptors that provide the detection of proprioception are located in the muscle spindles, in joints, and in skin. Proprioception is essential for any form of exploratory behaviour and in the control of balance, and is also known as kinaesthesia.

Tactile signals from the body travel from receptors, through peripheral nerves, to the dorsal root ganglion (analogous to the ventral root for motor pathway outputs as described in Section 1.3.4) where the first order sensory neurones are located. From here, there are two major ascending systems for somatic sensation: the dorsal column-medial lemniscus system and the anterolateral system (otherwise known as the somatosensory system) (Carpenter et al. 1968; for review see York, 1985; Barr & Kiernan, 1993). These pathways relay afferent information to the brain for three purposes: perception, arousal and motor control. The pathways are anatomically separate in the spinal cord and brainstem but become contiguous in the ventroposterior thalamus and the primary sensorimotor cortex. The two systems will be considered separately below and are shown in Figure 1.7.



medial lemniscus system spinothalamic system

Figure 1.7: General organisation of the dorsal column-medial lemniscus and anterolateral systems for the transmission of sensory information. See text for description.

1.4.3.1 The dorsal column-medial lemniscus system

The dorsal columns relay somatosensory information from the dorsal roots to the medulla concerning tactile sensation (especially fine discriminative aspects), vibration sense and proprioception (Wall, 1970). The main receptors involved are the Meissner's corpuscles and Pacinian corpuscles which, via peripherally running fibres, convey discriminative tactile sensation and vibration respectively to the dorsal root ganglia. They run ipsilaterally up the spinal cord via the (posterior) dorsal columns and divide into two fascicles, the medial 'gracile' and lateral 'cuneate' fascicle, in the upper level of the spinal cord (Petit, 1972; Rustioni, 1973; Rustioni & Kaufman, 1977). The fascicles then terminate in the lower medulla in the gracile and cuneate nuclei (collectively called the dorsal column nuclei, where second order sensory neurones are located). It is at this point that the fibres cross over the midline and assume the name of 'internal arcuate fibres'. On the contralateral side of the medulla the fibres coalesce and, by means of a brainstem pathway called the medial lemniscus, information is relayed first to the contralateral ventral posterior nucleus of the thalamus (Domino et al. 1965; Willis & Coggeshall, 1978) and then to the anterior parietal lobe (S-I) via the posterior limb of the

internal capsule for detection and interpretation of sensation (Mountcastle, 1974); for a more detailed review of the medial lemniscus system refer to (Norton, 1968; Mountcastle et al. 1969; Wall, 1970).

At all sections along the system, the fibres are arranged somatotopically (Wall, 1970). Tactile information from the arms and legs is conveyed via subdivisions in the dorsal columns; information from the arms is relayed in the cuneate fascicles and that from the legs in the gracile fascicles (York, 1985). In contrast, proprioceptive information for the arms and legs follows different paths to the medulla (Ross et al. 1979), probably mediated via group 1 muscle afferents (Oscarsson & Rosen, 1966; Landgren & Silfvenius, 1971; Phillips et al. 1971; Heath et al. 1976). For the arms, proprioception is conveyed in a similar manner to that of tactile sensation (via the cuneate fascicles to the contralateral medial lemniscus) (Oscarsson & Rosen, 1963; 1966). Proprioceptive information from the legs, however, is relayed in Clark's column (a column of large cells on the medial side of the dorsal horn in segments C8 through L3) by the axons of neurones in the nucleus dorsalis, which then synapse on neurones in the medulla (called nucleus Z) (Willis & Coggeshall, 1978). Here, some fibres project to the cerebellum via the dorsal spinocerebellar tract whereas other fibres give rise to internal arcuate fibres, crossing the midline, and join the contralateral medial lemniscus (Landgren & Silfvenius, 1971; Magherini et al. 1975).

1.4.3.2 The anterolateral system

The anterolateral system mainly conveys information regarding pain and temperature, although it is known also to have a minor role in crude tactile sense and proprioception (Cook et al. 1984). The receptors used for the detection of such sensory modalities are the nociceptors for pain, free nerve endings for temperature, and Merkel, Meissner's, Pacinian, and Ruffini endings for touch and proprioception. Both the anterolateral and dorsal column-medial lemniscus system are parallel ascending systems. This has the advantage of a degree of redundancy, so if one tract is damaged, the other can provide residual perceptual capability. Kaas (1997) however, demonstrated in monkeys that tactile and motor abilities that remain after specific dorsal column lesions depend entirely on the potentiation of spared dorsal column afferents or brain and spinal cord circuits, and not on functional substitution from the anterolateral tract. Anatomically, the anterolateral and medial lemniscus systems differ in three respects (Figure 1.7):

- ascending fibres of the anterolateral system cross at the level of the spinal cord via the anterior white commissure, while corresponding fibres in the dorsal column-medial lemniscus system cross in the medulla. Proceeding superiorly, neuronal fibres continue to join the internal aspect of the anterolateral tract, forcing somatotopy within the tract. Fibres are ordered such that those conveying sensation from the leg are layered parallel to and superficial to those from the chest and arm, which are superficial to those from the head.
- fibres of the anterolateral system originate in the dorsal horn and therefore they are neurones that are post-synaptic to the primary afferent fibres. Most axons in the dorsal columns are collaterals of the primary afferent fibres.
- most axons in the medial lemniscus terminate in the thalamus, but anterolateral fibres terminate throughout the brainstem in addition to the thalamus.

These points are summarised in Table 1.1.

The anterolateral system consists of three major pathways distinguished by their sites of termination. For the purpose of this thesis only the main spinothalamic tract, which relays information from the spinal cord to the brain, will be considered (for a detailed review of this tract see Hodge & Apkarian, 1990). After decussating in the spinal cord, the spinothalamic tract ascends through the brainstem. The tract is located on the lateral aspect of the medulla (called the lateral funiculus), clearly separate from the medial lemniscus, which is located on the midline. The two pathways also remain distinct in the pons but unite at the level of the midbrain, remaining segregated laterally. Finally, the fibres of the spinothalamic tract terminate on three regions in the thalamus: the posterior nuclei, the intralaminar nuclei, and the ventral posterior nucleus. These regions, via the posterior limb of the internal capsule, terminate on the posterior parietal region, the brainstem and other regions of the cortex, and the S-I and S-II cortex, respectively.

	Anterolateral system	Dorsal column-medial lemniscus system
Sensory modalities	Pain, temperature and crude touch	Tactile sensation, proprioception and vibration sense
Location in spinal cord	Anterolateral column	Dorsal column
Level of decussation	Spinal cord	Medulla
Origin of fibres	Dorsal horn	Collaterals of dorsal horn
Termination of fibres	Brainstem Thalamic nuclei	Thalamic nuclei
Cortical projections	S-I, S-II and posterior parietal cortex	S-I, S-II and posterior parietal cortex

Table 1.1: Summary of the two major ascending sensory systems

1.4.3.3 The ipsilateral sensory pathway in the normal individual

A number of sensory responses have been observed in the cortex ipsilateral as well as contralateral to the stimulus (Zulch, 1974; Lueders et al. 1984; 1986; Allison et al. 1989b; Schnitzler et al. 1995; Noachtar et al. 1997). However a number of studies have failed to identify an ipsilateral sensory pathway (Lueders et al. 1983; Wood et al. 1988; Allison et al. 1989a). Unilateral sensory lesions in animals and man have been shown to result in ipsilateral, in addition to contralateral, sensory deficits (for example Semmes & Mishkin, 1965). The presence of such responses is thought to be due to the existence of ipsilateral ascending sensory pathways. Such ipsilateral sensory projections are thought to exist in the spinothalamic tract (Andersson, 1962; Zulch, 1974; Lyubimov et al. 1980); however, their existence in the medial lemniscus system has not been established. The fact that the spinothalamic pathway includes elements with ipsilateral and contralateral receptive fields suggests that it is the source of at least part of the ipsilateral cortical projection, although whether it accounts for the entire projection is still in question (Semmes & Mishkin, 1965). Other studies refute the notion that the spinothalamic tract contributes to the generation of cortical ipsilateral sensory responses (Kakigi & Shibasaki, 1991). The spinocerebellar pathway has been suggested as an alternative pathway (Noachtar et al. 1997). It is clear from the literature that the presence and function of an ipsilateral sensory projection in the normal human is still in doubt.

1.5 Reorganisation of sensorimotor function in animals and man

In the last 15 years, there has been a considerable shift from the original idea of a 'hard-wired' brain (Hubel & Wiesel, 1962), to the fact that there is neuronal plasticity (the capacity to remould connections within the nervous system), first demonstrated by (Merzenich et al. 1983). Now the notion that neuronal plasticity exists is beyond doubt - not only in the brain's response to injury or disease but also in normal brain development in response to experience (such as Sasaki & Gemba, 1987; Stein & Glasier, 1992; Bear & Malenka, 1994; Kolb & Whishaw, 1998), and to changing external environment (for example O'Leary et al. 1994; Classen et al. 1998a).

A wealth of evidence now exists for plastic changes in the cortex following brain and also peripheral nerve damage (among others Merzenich et al. 1984; Donoghue et al. 1990; Frackowiak et al. 1991; Merzenich & Jenkins, 1993; Kew et al. 1994; Hedstrom et al. 1996). Research has recently concentrated on determining the underlying cortical process of plasticity: in particular, does it occur through the formation of new neural connections or merely by unmasking existing, functionally inactive, connections? Despite extensive documentation of its existence in the past decade, the nature of the processes by which the plasticity of cortical representations occurs is only just beginning to be understood. Studies have been contradictory, with cortical reorganisation in some cases appearing too quickly to be due to the formation of new connections (Ramachandran et al. 1992; Ramachandran, 1993), and yet in other studies, over too large an area (up to 14 mm) to be accounted for by any pre-existing pathways (Pons et al. 1991). Many groups have promoted the notion of axonal sprouting and synaptic proliferation to account for at least the small-scale (few millimetres) plasticity observed in both animals and man (for example Kaas et al. 1983; Ramachandran, 1993; Darian Smith & Gilbert, 1995; Seitz et al. 1995; Kolb & Whishaw, 1998; Xerri et al. 1998). Alternatively both the rapid dynamic and slow adaptive 'plasticity' processes mentioned above could occur together or in sequence over the full time course of reorganisation (Gilbert & Wiesel, 1992; Clarey et al. 1996; see review by Ramachandran, 1993; Cusick, 1996).

Further evidence highlights the presence of horizontal (otherwise known as lateral or reciprocal) connections that link neurones of the cortex over a distance of up to 6 to 8 millimetres (Jacobs & Donoghue, 1991; Hess & Donoghue, 1994; Donoghue, 1995; Hess et al. 1996; Huntley, 1997). Studies have confirmed the activation of these connections for the expansion of a receptive field in any part of the cortex when one area

is silenced (Kaas, 1991; Gilbert & Wiesel, 1992; Darian Smith & Gilbert, 1994; Gilbert et al. 1996). Collectively, these studies not only confirm the potential for rapid reorganisation of the primary motor and sensory cortex, but also show that the extent of this early reorganisation follows from the pattern of intrinsic connections already present in the cortical areas. This concept has been referred to as 'filling-in'. The loss of a main function may be partially unnoticed due to plasticity occurring in other cortical areas which overcomes the deficit (Barinaga, 1992; Ramachandran, 1993). There are numerous reports of changes in somatotopic maps, for example following peripheral deafferentation in a variety of mammalian species (for review see Cusick, 1996). Based on the idea that one cortical neurone receives many inputs from a region on the skin's surface constituting the receptive field, it has also been suggested that in a mature brain a cell's receptive field could change without changing the anatomical connections that provide input to the neurone (Sur, 1995). In the developing brain, there may also be physiological changes in synaptic efficacy which lead to subsequent anatomical changes (Sur, 1995). It is thought, however, that the basic topography of horizontal connectivity may impose some fundamental limitations on the extent of reorganisation in some cortical areas, which may be independent of the time course involved (Darian Smith & Gilbert, 1995; Huntley, 1997).

A complete understanding of mechanisms underlying reorganisation requires investigations of the myriad of changes in synaptic and intracellular signalling pathways that follow peripheral nerve injury or learning. For example, numerous studies have begun to address the neurochemical responses of the cortical and thalamic somatosensory and motor systems to injury or learning (for example Cusick, 1991; Garraghty et al. 1991; Spear, 1996; Schwartz, 1998). This is a topic under intensive investigation, particularly with the possibility that neurotrophin or other neurochemicals may enhance functional and anatomical compensation if administered to animals and/or humans with brain lesions (Stein & Sabel, 1988; Steinberg & Augustine, 1997).

It is possible that more than one of the above mechanisms is involved in functional reorganisation, particularly since several types of cortical reorganisation have been shown to occur. These include:

1. The local transfer of cortical function in the vicinity of the lesion, over a few millimetres or less. Recovery of function in stroke patients may be associated with the representation of sensory or motor function in areas immediately adjacent to the site of the lesion (for example Cao et al. 1998). Similarly, Evarts (1982) suggested that recovery from restricted cortical lesions may involve a shift in cortical functions away

from a damaged focus and into adjacent intact areas. Many studies using a variety of techniques in normal animals and man have also demonstrated the expansion of receptive fields in response to regular sensory stimuli or complex motor tasks to accommodate the change in functional demand, thus confirming that this form of cortical plasticity may occur (for example Grafton et al. 1992a; Nudo et al. 1992; Pascual Leone et al. 1994; Roullier et al. 1998).

2. A shift in the primary sensorimotor function to more remote sites in the same hemisphere. This may occur when a large area of cortex is damaged and there is insufficient surviving tissue around the affected site to allow cortical reorganisation in close proximity to the lesion (as described above). Such plasticity can take place over several centimetres, the areas involved more often being more closely related by function than by proximity. Thus, it has been shown that secondary cortical sensory and motor areas (and by implication their efferent corticocortical and corticosubcortical pathways) may compensate for the disruption of the output of the primary cortical areas (for example Weiller et al. 1993). This is theoretically possible because of the large number of parallel and independent inputs to and outputs from the motor and sensory cortices. In addition, areas not normally directly involved in sensorimotor control may be activated, such as the prefrontal, anterior cingulate, and inferior parietal cortices (for example Chollet et al. 1991; Frackowiak et al. 1991; Muller et al. 1998).

3. A process of inter-hemispheric reorganisation of function (as opposed to the intra-hemispheric mechanisms outlined above). Many studies have now suggested that uncrossed, ipsilateral cortico-spinal fibres may assume importance in pathological conditions (for example Jung & Dietz, 1975; Maegaki et al. 1995). In humans, the role of ipsilateral motor pathways has been highlighted in the recovery of contralateral motor function in response to a variety of brain lesions, such as hemispherectomy, stroke, tumours or agenesis of the corpus callosum (among others, Jeeves & Silver, 1988; Farmer et al. 1990; Cohen et al. 1991a; Weiller et al. 1992; Carr et al. 1993; Maegaki et al. 1995). Such ipsilateral fibres have been demonstrated to project to both primary and secondary sensorimotor areas in the unaffected hemisphere (Sabatini et al. 1995; Cao et al. 1998). The developmental origin of the pathways mediating the ipsilateral response is, however, still unclear. One idea stems from anatomical studies demonstrating the development of novel, aberrant corticospinal pathways following early unilateral central nervous system lesions (Hicks & D'Amato, 1970; Farmer et al. 1990; Maegaki et al. 1995). These anomalous axons arise from axonal sprouting in the undamaged ipsilateral motor cortex. An alternative theory suggests that the ipsilateral hemisphere compensates for the sensory and/or motor function in the paretic limb via pre-existing ipsilateral

corticospinal pathways which normally get lost during early development (Benecke et al. 1991). These pathways account for approximately 25% of the descending corticospinal fibres, as previously described in Section 1.3.4.1. Such pathways are thought to be enhanced or stabilised by brain damage, particularly if damage is sustained early in life. Finally both types of change resulting in ipsilateral projections (pre-existing fibres and axonal sprouting) may co-exist (Carr et al. 1993; Maegaki et al. 1997). One other possible mechanism is the double-crossing of normally crossed corticospinal fibres, possibly at the level of the thalamus (Chen et al. 1997a). There is additional evidence that transcallosal projections from the cortex of one hemisphere to homologous regions of the opposite hemisphere are predominantly inhibitory (Ferbert et al. 1992; Muller et al. 1997a), also mentioned in Section 1.3.1). Such inhibitory influences may also be mediated below the cortical level, even at multiple levels along the neuroaxis (Gerloff et al. 1998). From these findings, it follows that damage to the cortex of one hemisphere or lower down in the neuroaxis might conceivably lead to disinhibition of the cortical motor areas in the opposite hemisphere. Indeed, studies of acallosal patients have suggested an enhanced development of uncrossed ipsilateral pathways when the normal inhibitory action of the callosum in suppressing such ipsilateral output is absent, leaving competition present with the normal contralateral output for controlling, say, finger movement (Jeeves & Silver, 1988). This aberrant process may result in mirror movements in the patient (see Section 5.2.2.4 of Chapter 5). In addition to motor reorganisation, ipsilateral connections are also thought to account for residual sensory function. Such ipsilateral sensory pathways may possibly exist through the spinothalamic system (refer to Section 1.4.3.3).

Anatomical changes in the cortex contralateral to the cortical damage have been shown to occur in adult rats, adding further evidence for the capacity for reorganisation of function between hemispheres (Jones & Schallert, 1989; 1992). The neuronal growth (specifically dendritic arborization of layer V pyramidal neurones) reported to be responsible for such plasticity was found to be dependent upon the use of the non-impaired forelimb (Jones & Schallert, 1994). The overgrowth of dendrites was related in time to the disuse of the contralesional forelimb and over-reliance on the ipsilateral forelimb for postural and exploratory movements. However, the authors also noted that forelimb overuse per se was not sufficient to yield arborization increases; the presence of brain damage, perhaps specifically a lesion in the opposite cortex, also appears to be necessary. It therefore seems plausible that a cortical lesion initiates a process that prepares the contralateral cortex for behaviourally-mediated neural plasticity (perhaps via the terminal degradation of transcallosal afferents originating from the lesioned side). In addition, there appeared to be a significant learning component involved for the

arborization increases, as lesion-induced behavioural changes occurred in the ipsilesional forelimb (Jones & Schallert, 1994). Further research suggested an increase in the number of synapses per neurone and the volume and membrane surface area of dendritic processes per neurone to be the underlying compensatory changes in the cortex (Jones et al. 1996).

Together, these experiments indicate that plasticity occurring within the cortex itself is a very important, if not the primary, basis for certain types of cortical reorganisation. However, other contributions to plasticity may also occur involving sites elsewhere in the central nervous system. Reorganisation has been shown at each level of the neuraxis, such as the spinal, brainstem and thalamic sites, which may influence higher cortical representation patterns (Wall & Egger, 1971; Devor & Wall, 1981; Garraghty & Kaas, 1991; Florence et al. 1993; Pettit & Schwark, 1993; Faggin et al. 1997). The extent of reorganisation in these structures, however, has been suggested to be small (Garraghty & Kaas, 1992; Schwegler et al. 1995; Dinse et al. 1997). Future research may elucidate the relative contributions of different sites of plasticity and the experimental conditions in which they apply differentially. One possibility is that the first and primary site of reorganisation is in the cortex and that, with time, reorganisation occurs in subcortical areas in a retrograde fashion.

The extent of brain plasticity following brain injury is thought to be dependent on a number of factors. These include the age of the individual at the time of injury, size and topography of the brain lesion, whether the lesion is neurologically symptomatic or asymptomatic, growth rate of the lesion, maturational state of the injured brain system, integrity of the areas surrounding and contralateral to the lesion, and pharmacological effects (for review see Chugani et al. 1996). Many studies have demonstrated reorganisation of sensorimotor function in both adults and children (for example Mogilner et al. 1993; Muller et al. 1997a). Several studies have shown that sensorimotor recovery and reorganisation is particularly remarkable if the brain is damaged early in life when the brain is still developing and cortical connections still being laid down (for example (Vargha-Khadem et al. 1985; Benecke et al. 1991; Carr et al. 1993; Kolb, 1995; Chugani et al. 1996; Muller et al. 1997a). Further evidence comes from younger children following callosotomy, who appear to be considerably less affected than older children by the interruption of callosal transmission on tests of unilateral discrimination and interhemispheric transfer of tactile information (Lassonde et al. 1986). The authors of the study speculate that older children depend more extensively on contralateral pathways for sensorimotor function, whereas the younger children group still retained ipsilateral pathways to assist in such function (also suggested by Muller et al. 1997a).

The notion that the developing brain has a higher capacity for brain plasticity compared to the adult state is known as the Kennard effect (Kennard, 1938; Finger & Wolf, 1988).

1.6 Aims of this study

The aim of the research described in this thesis was to use three non-invasive approaches to investigate sensorimotor function in children with brain damage. The three approaches employed were functional MRI (fMRI), somatosensory evoked potentials (SEPs), and behavioural measures of sensorimotor function. fMRI has the distinct advantage over most methods of high spatial resolution (millimetres). SEP recordings are known for their high temporal resolution (milliseconds), the spatial resolution of the technique being limited to the order of centimetres. These techniques have particular advantages over invasive methods used to investigate brain function, as activation studies can be easily carried out in children as well as in adults and are repeatable. Finally, neuropsychological measures of sensorimotor function provide quantitative information about the extent of residual function following brain damage.

The specific aims of the work presented in this thesis are as follows:

- To establish suitable experimental paradigms, combining all three approaches, for the investigation of children who have sensory and/or motor impairments (Chapters 2 to 6).
- To identify the cortical substrate subserving residual sensorimotor function in children with unilateral brain damage involving a part of, or the entire, sensorimotor system in one hemisphere (Chapters 7 and 8).
- To use fMRI as a non-invasive tool, alongside other invasive traditional cortical mapping techniques, to locate the primary sensorimotor hand area in paediatric patients prior to neurosurgery (Chapter 9).

Chapter 2: Functional magnetic resonance imaging - principles and functional sensorimotor studies

2.1 Introduction

In this chapter the principles of functional MRI (fMRI) are described, with particular emphasis on the spatial and temporal resolution of the method. In addition, a literature review is given of previous fMRI studies of sensorimotor function in normal controls. A variety of sensory and motor paradigms have been used, including active movement tasks, passive movement tasks, and electrical stimulation of peripheral nerves, each of which will be addressed in turn.

2.2 Principles of functional magnetic resonance imaging

The first study of functional brain mapping in humans with magnetic resonance imaging (MRI) was carried out by Belliveau et al. (1991). This initial study involved the investigation of the visual system, using a photic stimulus following the injection of a bolus of a paramagnetic contrast agent (Gd-DTPA) into the antecubital vein to act as a marker of cerebral blood volume. Before, during and after the administration of the bolus, single slice echo-planar images of the brain in the plane of the calcarine fissure were obtained at 750 ms intervals to monitor the passage of the bolus in the brain. From the time course of the detected water signal intensity changes (caused by the magnetic susceptibility effects of Gd-DTPA) it was possible to generate images that reflect relative cerebral blood volume. Consistent increases of up to 30% of blood volume in the primary visual cortex were observed compared to the resting state.

In 1990, two studies by Ogawa et al. of rodent brains at high magnetic field strength showed proton MRI signal intensity alterations related to blood oxygenation in regions close to blood vessels (Ogawa et al. 1990a&b). The same finding was demonstrated in the cat brain by Turner et al. (1991). Such studies suggested that it might be possible to perform functional imaging studies without the need for an externally administered contrast agent, but by making use of an endogenous source of contrast. This phenomenon, termed Blood Oxygenation Level Dependent (BOLD) contrast, has now been extensively exploited in human studies. fMRI using BOLD contrast has demonstrated haemodynamic changes within the brain that are associated with activation

of the visual, motor, language, memory and other brain systems (for example of a recent review see (Di Salle et al. 1999).

Prior to the studies of Ogawa et al. (1990a&b), PET studies had shown that during neuronal activity there is an increase in the local relative cerebral blood flow (rCBF) and volume, with relatively little change in oxygen consumption (Fox & Raichle, 1986; Fox et al. 1988; Chen et al. 1998). In this situation, the venous blood becomes more oxygenated local to any activation, with a net conversion of deoxyhaemoglobin to oxyhaemoglobin (Bandettini et al. 1992; Frahm et al. 1993; Kwong et al. 1992; Ogawa et al. 1992). There are magnetic susceptibility effects associated with this decrease in deoxyhaemoglobin concentration. On deoxygenation of haemoglobin, the electron spin state of the haem Fe^{2+} changes, such that diamagnetic oxyhaemoglobin (no unpaired electrons) becomes paramagnetic deoxyhaemoglobin (4 unpaired electrons). This paramagnetism influences the proton signals of neighbouring molecules, including those of water, as a result of local field gradients generated in and around the blood vessels (Figure 2.1). These local gradients may extend significantly into the surrounding tissue (Figure 2.1), causing local signal reduction on appropriately weighted images (see below). A reduction in the local field gradients in 'activated' tissue, resulting in a signal increase, forms the basis of BOLD contrast in fMRI.

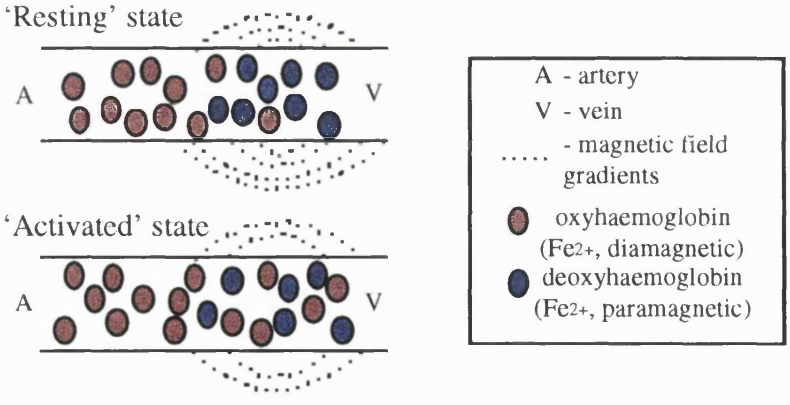


Figure 2.1: Effect of blood flow and deoxy/oxyhaemoglobin concentration changes on the magnetic field gradients in and around the surrounding blood vessels in an 'activated' compared to 'resting' brain state. A lower concentration of paramagnetic deoxyhaemoglobin in activated tissue results in smaller local magnetic field gradients, an increase in T_2^*, and hence an increase in signal intensity in these regions.

The MRI signal changes that are detected in fMRI reflect changes in the effective decay rate of the transverse magnetisation (i.e. $1/T_2^*$) which arise from changes in the local field gradients that occur with activation. BOLD fMRI is thus based predominantly on a T_2^* effect, in which the local decrease in the concentration of paramagnetic ions within

the activated tissue increases the apparent transverse relaxation time (T_2^*) (as a result of a decreased dephasing of the proton spins) (Ogawa et al. 1990b). As a consequence, this region has an overall higher signal in the corresponding voxel(s) of the T_2^*-weighted image (for review see Moseley et al. 1996).

T_2^*-weighted images are generated by the use of gradient echoes which, unlike spin echoes, do not rephase the dephasing effects of local field inhomogeneities associated with the presence of deoxyhaemoglobin. In order to optimise the detection of changes in local field inhomogeneities associated with the changes in deoxyhaemoglobin /oxyhaemoglobin levels during cerebral activation, the static external magnetic field (B_0) homogeneity must be adjusted in order to minimise any background field inhomogeneities. This optimisation is achieved by 'shimming' the B_0 field, so permitting the detection of focal changes in magnetic field gradients in the tissues.

2.2.1 Sensitivity

fMRI studies are based on the difference between images acquired during the performance of a task and another physiological state (for example a resting state). As described above, this difference identifies regions of 'activation' which reflect local changes in venous oxygenation and a signal intensity change in T_2^*-weighted images. The question arises as to the sensitivity of fMRI, i.e. its ability to detect small activations over the level of detected noise. Initial fMRI studies were carried out using visual and motor tasks. These tasks provide an appropriate means of establishing and validating the method because they are relatively well characterised and, more importantly, the haemodynamic changes (and hence signal intensity changes) associated with such tasks are likely to be considerably greater than those associated with higher cognitive functions. The BOLD effect for any task is small compared to the overall signal intensity, usually between 2-6% for a motor or visual task in a 1.5T system (Bandettini et al. 1992; Kwong et al. 1992). Numerous studies have now been carried out to localise the cortical areas involved in mental imagery and other higher cognitive tasks (for example Porro et al. 1996; Booth et al. 1999) which may be associated with very small haemodynamic changes and hence with small percentage changes in signal intensity. While the detection of signal intensity changes of 1% or less is feasible, it relies on a number of technical considerations such as the stability of the machine performance, voxel volume, and post-processing methods of image realignment and statistical analysis. Focal stimulus-correlated changes in signal intensity have been found to be largely confined to grey matter tissue within the cortex (where blood accounts for

6% of the tissue mass) (Belliveau et al. 1991; Kwong et al. 1992). Activation has been seen in white matter pathways such as the posterior limb of the internal capsule, but so far only at high field strength (4 Tesla) (Maldjian et al. 1999). Thus, any modelling of the observed signal effects must consider the blood vessels and haemodynamic changes that are characteristic specifically of the activated grey matter regions.

2.2.2 Spatial Resolution

An important advantage of fMRI is that it has greater spatial resolution than many techniques for the localisation of cortical function, in the order of millimetres. However, the spatial resolution of fMRI still appears somewhat coarse compared with that of conventional MRI techniques.

It is not yet clear how well the increase in delivery of blood to brain tissue is spatially matched to the increased metabolic demand caused by neural electrochemical activity (specifically in grey matter). As mentioned above, the source of the activation signal with fMRI is located in the vascular bed and surrounding perivascular tissues, particularly at the distal capillary and venous level. At present, however, there remains some doubt over the exact location of the spins which are the source of the BOLD effect. Optical imaging techniques have shown that blood vessels during stimulation become more highly oxygenated over an area of a few millimetres in diameter around the site of neuronal activity (Malonek & Grinvald, 1996). This imposes a spatial resolution limit for fMRI as, despite the high intrinsic resolution of MRI, the source of the vascular response underlying the signal change is determined by the extent to which the BOLD signal is influenced by the increased blood flow and spreads beyond the area of activated cortical neurones (Malonek & Grinvald, 1996). fMRI studies have shown that decreasing the voxel size reduces the apparent size of the activated region and increases the signal change (by minimising partial volume effects) (for example Frahm et al. 1993). The question arises as to whether this offers new information with regards to brain function or merely reflects localised venous drainage already characterised at low resolution. Recently Thulborn et al. (1999) carried out comparative fMRI studies at 3T with low (voxel size = $3.1 \times 3.1 \times 3 mm^3$) and high (voxel size = $0.8 \times 1.6 \times 3 mm^3$) spatial resolution during visually-guided saccades. The high resolution activation maps showed discrete multifocal cortical responses in the frontal eye fields that were not resolved at low resolution. The response was localised to the grey matter, with no observed contribution from small or large veins. In summary, there appear to be advantages to studying cortical activation using fMRI at high spatial resolution which may reveal new

information about underlying neuronal responses, but the attainable resolution will be limited ultimately by the nature of the haemodynamic response that gives rise to the observed signal changes.

A number of studies have suggested that BOLD changes may be detected in the venous system several millimetres downstream from the site of neuronal activity (Boxerman et al. 1995). This may give rise to a high signal intensity in activation maps from veins draining wider cortical regions than those actually activated (Lai et al. 1993; Wen et al. 1993; Huu Le et al. 1995; Nakajima et al. 1995; Itagaki et al. 1996). The distinction between signal change stemming from large veins running along sulci and smaller vessels in grey matter is an important one because veins that run along sulci receive blood from a large volume of cortex and therefore poorly localise neural metabolism. In addition, signal increases during neural activation can also occur due to an apparent T_1 effect in the larger blood vessels (Kwong et al. 1992). In principle, flowing blood is not subjected to the same radiofrequency pulses as stationary tissue. As fresh unsaturated blood moves into the imaging slice it yields higher signal intensity (hence apparent reduction in T_1) than blood which has been repeatedly excited by the previous slice selective radiofrequency pulses. It follows that large blood flow changes correlated with the stimulus can lead to an increased fMRI signal (Yamada et al. 1997). The presence of this effect and how it relates to neuronal activity has been paraphrased by the question 'brain or vein - oxygenation or flow' (Frahm et al. 1994). Some very large signal changes reported in the early fMRI experiments have since been shown to be due to T_1 flow effects (Lai et al. 1993; Duyn et al. 1994; Frahm et al. 1994; Segebarth et al. 1994; Hoogenraad et al. 1998), as opposed to resulting from BOLD signal changes.

A number of methods have been reported for the differentiation of signals arising in capillaries in the cortical parenchyma from signals in large vessels caused by T_1 inflow as well as downstream BOLD effects. Mapping the macrovasculature, for example using angiographic techniques, will allow any increased signal intensity to be compared directly with the anatomical location of the draining vessels (for example Harrington & Downs, 1999; Hoogenraad et al. 1999). Ogawa et al. (1993) used radiofrequency-refocused spin-echo sequences with a relatively decreased sensitivity to larger vessels compared to T_2^*-weighted methods. Constable et al. (1994) showed that a fast spin-echo technique resulted in reduced apparent activation, in part due to a diminished inflow signal. This spin echo imaging technique was also initially developed for fMRI by other groups (Kwong et al. 1993; Turner et al. 1993). The major disadvantage of using spin-echo sequences in fMRI is the decreased sensitivity to intrinsic BOLD contrast compared to gradient-echo sequences (Bandettini et al. 1994), particularly at lower field strengths

(for example Ogawa et al. 1993). Lee et al. (1995) discriminated cortical parenchyma BOLD signal changes from those originating from large venous vessels by examining the temporal delay of each pixel's response to the stimulus. The signal changes in pixels anatomically associated with capillaries in grey matter were delayed between 4 and 8 seconds after the onset of the stimulus, compared to pixels within large vessels which were delayed from 8 to 14 seconds. Glover et al. (1996) developed a dual-echo interleaved spiral sequence, so allowing the separation of inflow from T_2^*-weighted components in two images. Other groups have sought to minimise inflow contribution by using long TR, small flip angles, and volume acquisitions (Haacke et al. 1994) or spatial presaturation (Duyn et al. 1994). There is also controversy over the contribution of intra- and extra- vascular local magnetic field gradients to the BOLD contrast (for example Ogawa et al. 1993; Boxerman et al. 1995). In general, it appears that the intravascular spins account for the majority of T_2^*-weighted fMRI signal change within the cortical tissue, even in regions where the vascular volume fractions are small (4-6%) (Boxerman et al. 1995).

2.2.3 Temporal Resolution

To a first approximation one can think of the observed haemodynamic response as a spatially and temporally smoothed version of the underlying neural activity. The temporal resolution of the technique may be limited by the imaging sequence or by the time dependence of the underlying physiological effects in response to a task. Many studies have shown that the increase in signal intensity on cortical activation occurs over several seconds (approximately 5 - 8 seconds from stimulus onset to 90% maximum) reflecting the gradual haemodynamic response of the brain (for example Belliveau et al. 1992; Blamire et al. 1992; Frahm et al. 1993; Kwong et al. 1992). Some studies have shown however that during the first 0.5-2 seconds of neuronal activation there is an initial transient decrease in regional signal intensity seen in fMRI (Ernst & Hennig, 1994; Hennig et al. 1995; Menon et al. 1995a&b; Le & Hu, 1996). The authors suggest that one of the likely mechanisms for this initial signal decrease is that the activated tissue takes up additional oxygen from the blood before there is a chance for the blood flow to increase, and so there is a proportionate deoxyhaemoglobin concentration increase (opposite to the BOLD signal change normally detected in fMRI). The detection of this signal decrease, in addition to the subsequent prolonged increase in signal intensity that has formed the basis of many fMRI studies, may provide a method for detecting cortical activation at higher temporal resolution. A recent study has investigated the relationship between CBF and haemoglobin concentration using imaging

spectroscopy (which allows selective measurement of both deoxy- and oxyhaemoglobin) and laser-Doppler flowmetry techniques (Malonek et al. 1997). It was found that the earliest haemodynamic changes were an increase in the concentration of deoxyhaemoglobin, the CBF increase lagging behind the increase in deoxyhaemoglobin concentration (by more than a second). These studies also showed that the early hemodynamic changes were more spatially localised than the delayed and less specific CBF response. This supports the findings described above of an initial transient decrease in regional signal intensity seen in fMRI.

One ongoing debate with respect to the mechanism of BOLD contrast is the underlying relationship between neuronal activity and other physiological parameters such as relative cerebral blood flow (rCBF), cerebral blood volume (CBV), oxygen metabolism and glucose metabolism. Controversies have emerged because of difficulties in interpreting the signals measured by different imaging techniques (for example, fMRI, PET, optical imaging, and SPECT) in terms of the characterisation and quantification of underlying physiological changes, and in selectively measuring haemodynamic changes (for example, deoxyhaemoglobin changes without rCBF changes) from each vascular compartment. Changes in rCBF have been correlated with presumed neuronal activity in a number of studies in the primary visual cortex (Fox & Raichle, 1986), primary auditory cortex (Price et al. 1992) and the primary sensorimotor cortex (Ibanez et al. 1995; Sadato et al. 1996b). There is also evidence, however, that at higher stimulus frequencies (greater than 4Hz) this relationship may be broken due to the rCBF reaching a maximal level in a particular cortical area (Ibanez et al. 1995). This plateau of rCBF is unlikely to be caused by maximal neuronal firing as several studies have demonstrated increased neuronal firing in response to much higher stimulus frequencies up to 40Hz (Hyvarinen et al. 1968). There have been a number of studies suggesting that the fMRI signal intensity is proportional to the rate of presentation and intensity of the stimulus and also to the rCBF from corresponding PET studies (Dettmers et al. 1996; Rao et al. 1996). Studies using a motor finger movement task have more recently identified that with frequencies above 2Hz there is a similar plateau found in both rCBF and fMRI activation (Sadato et al. 1997). There is also general agreement that the local cerebral metabolic rate of glucose (CMRglu), rCBF, and cerebral blood volume (CBV) are coupled at rest and during physiological stimulation. Changes of rCBF therefore reflect changes in glucose metabolism during stimulation, which in turn provides energy for neuronal activity (predominantly pre-synaptic activity) (for review see Jueptner & Weiller, 1995). The relative change in cerebral metabolic rate of oxygen ($CMRO_2$) during neuronal activity, on the other hand, is still undetermined. However, the BOLD effect in fMRI appears to depend on at least partial uncoupling between CBF and

$CMRO_2$ changes, and Kim et al. (1999) have suggested that $CMRO_2$ is increased significantly during visual stimulation, the magnitude of the change being 0.3-0.7 times the CBF change.

2.3 Investigations of sensorimotor function

Sensorimotor function has been extensively investigated since the original fMRI experiments in the early 1990s. Many of the fMRI studies to date have confirmed results obtained using other techniques, in particular PET imaging. As a consequence, in this review of fMRI investigations of sensorimotor function, comparative literature from PET imaging and other techniques is also mentioned. Several anatomical methods have been developed to identify the central sulcus and sensorimotor area using CT or structural MRI (Kido et al. 1980; Ebeling et al. 1986; Steinmetz et al. 1990; Rumeau et al. 1994; Naidich et al. 1995). But although the typical anatomy of the rolandic region has been defined (see Sections 1.3.1 and 1.4.1 of Chapter 1), identification of the sensory and motor structures can still be difficult in some cases, as reflected by the high variability of results obtained by different observers (Sobel et al. 1993). This in turn indicates the importance of additional landmarks or new imaging methods to locate these structures more reliably (Yousry et al. 1995; 1997).

A frequent observation in fMRI studies of human sensory and motor representation is that signal changes are found not only along the pre-central or post-central gyrus, but also and often predominantly within the central sulcus. The reasons for this may be three-fold. Firstly, signal changes may be from larger draining veins within the central sulcus (Sanes et al. 1995). Secondly, because a motor task produces tactile and proprioceptive sensory feedback (Yetkin et al. 1995), activation in both the sensory and motor region is anticipated. Similarly, involuntary muscle activity during tactile sensory stimulation must not be excluded. This makes the spatial distinction between responses from the 'sensory' or 'motor' cortex difficult. Thirdly, several studies have documented motor hand activation not only in the precentral gyrus but also in the anterior wall of the postcentral gyrus (Uematsu et al. 1992a; Puce, 1995; Yousry et al. 1995; Kahn et al. 1996). This suggests an overlap of the sensory and motor function in the central area which has also been identified using subdural grid stimulation (Uematsu et al. 1992b; Nii et al. 1996; see Sections 1.3.1 and 1.4.1 of Chapter 1). Care should be taken therefore in investigating the sensory or motor cortex specifically and in interpreting results in the literature. In fact, results with the sensory and motor tasks are sufficiently

similar so that they may be used interchangeably to identify the sensorimotor cortex (Yetkin et al. 1995; Mueller et al. 1997).

2.3.1 Activation paradigms to investigate sensory and motor function

The following sections briefly summarise the literature that has accumulated on sensory and motor activation paradigms using fMRI. Attention is paid to three areas that are particularly relevant to the research described in this thesis; simple versus complex movements, passive movement, and electrical median nerve stimulation.

2.3.1.1 Complex versus simple motor tasks involving the hand

Both simple and complex motor paradigms have been used to detect areas responsible for hand motor control. Using fMRI and PET techniques, simple uncued movements, such as repetitive opening and closing of the hand (Remy et al. 1994; Yousry et al. 1995; Fukunaga et al. 1997), squeezing of a sponge (Puce et al. 1995), tapping of all fingers in unison except for the thumb (Rao et al. 1993, 1995), or finger to thumb opposition (Jack et al. 1994), have shown activation in the contralateral primary motor cortex. More complex movements such as sequential tapping of the fingers in a predetermined fixed order or unnatural 'individuated' finger movements (for example singularly tapping the middle finger onto the thumb), may additionally activate all, or a selection of, the ipsilateral primary motor cortex, the supplementary motor area, the premotor, somatosensory cortex bilaterally and parietal cortex bilaterally, as detected by ^{133}Xe-labelled rCBF measurements (Roland et al. 1980), PET imaging (Shibasaki et al. 1993; Sadato et al. 1996a; Kawashima et al. 1998) or fMRI (Kim et al. 1993a; Rao et al. 1993; Pujol et al. 1996; Wexler et al. 1997). The precise mechanism by which the motor cortex individuates movement (such as the movement of an isolated finger) is not clearly understood, but one model predicts that the more individuated the movement of the fingers, the more neurones should be activated in the motor cortex (Scheiber, 1990; Remy et al. 1994). In several studies, activation in the ipsilateral primary motor cortex was located more anteriorly than in the contralateral primary motor cortex (Sadato et al. 1996a). The authors attributed this difference to the absence of sensory feedback on the ipsilateral side. Another possibility is that the ipsilateral representation of the hand is truly located anterior to the representation of the contralateral hand (Wassermann et al. 1994). Other studies, however, have not disclosed any difference between cortical responses to simple or complex movements (Fox et al. 1985; Colebatch et al. 1991). The discrepancies in these results may be a consequence of the nature of the motor tasks

used in different studies (Shibasaki et al. 1993; Remy et al. 1994). Certainly, pacing even simple movements in response to an external cue (Roland et al. 1980; Fox et al. 1985; Colebatch et al. 1991) may require a higher level of programming than that required during self-paced movements (Remy et al. 1994). In a number of more recent PET studies examining brain activation patterns with simple repetitive sequential finger movements of different lengths, specific cortical areas were found to be recruited to assist in the storage of motor sequences in spatial working memory, for example the ipsilateral premotor area, bilateral posterior parietal areas and the precuneus (Sadato et al. 1996a; Catalan et al. 1998).

There have also been reports that the primary motor area may be critically involved in the processing of motor sequences and in particular complex sequences (Shibasaki et al. 1993; Corwell et al. 1996; Manganotti et al. 1997; for review see Kawashima & Fukuda, 1994). Subregions have been discovered within the M1 hand area which are related to preparatory activity and others that change their activity with the learning of new motor skills (Kitamura et al. 1993; Kawashima et al. 1994). Karni et al. (1995) and Pascual Leone et al. (1995), using fMRI and TMS respectively, found enlargements of the M1 cortex during the long-term learning of a motor sequence. A recent study has implied that the primary motor cortex is also involved in the initial 'fast' learning of motor sequences, suggesting that the primary cortical area may control short as well as long-term motor learning (Karni et al. 1998). These studies have challenged the traditional concept of the primary motor cortex having a simple executive role. There appear from the above literature, therefore, to be advantages for the use of a more complex functional task which will activate more areas of the cerebral cortex and increase the level of activation within specific areas, including the primary motor cortex.

Differences in brain activity with simple and complex sensory stimuli have also been demonstrated using fMRI (Tsunoda et al. 1996). Signal increases in the contralateral sensorimotor area have been seen following simple sensory compressed air stimuli. In contrast, activity in the contra- and/or ipsilateral sensorimotor area was observed during complex sensory stimulation consisting of the formation of figures drawn on the subjects palm. In addition, some volunteers exhibited signal increases in the parietal or frontal association cortex only when attention was paid to the stimulus. A comparatively simple motor task (tapping of the fingers of one hand) resulted in activation in the contralateral sensorimotor area and occasionally in the ipsilateral paracentral region and supplementary motor area.

2.3.1.2 Passive movement

There have been few reported studies that have concentrated on fMRI sensorimotor activation in response to passive movement of body parts. Investigations into passive movement versus active movement have provided insight into the contribution of sensory feedback during motor control. Several studies have attempted to address the hypothesis that cortico-spinal neurones in the primary motor cortex fire during passive movement by comparing the task directly with active motor tasks. Krams et al. (1996, 1997), using PET, noted in an active and passive task of index finger to thumb opposition that contralateral primary sensory and motor activation occurred. This activation was very similar in appearance in the two tasks both in normal adult controls (Krams et al. 1996, 1997) and in patients with X-linked Kallmann's syndrome displaying mirror movements (Krams et al. 1997). They concluded that 'activation in the primary motor cortex may partly reflect synaptic activity related to afferent sensory feedback'. This has also been shown in other PET and fMRI studies in normal controls (Zeffiro & Hallett, 1992; Bernard et al. 1996). In another fMRI study, however, the most striking difference between active and passive motor tasks was the recruitment of the contralateral premotor and ipsilateral primary motor cortex only in active movement (Goran et al. 1996). Other studies have suggested that the major difference was the additional involvement of the supplementary motor area for the voluntary active aspects of movement (Bernard et al. 1996; Mima et al. 1997). Recently, Mima et al. (1999) also reported different areas of fMRI activation in association with an active and passive movement task. Passive movement elicited a weak and spatially limited brain activation map in the contralateral primary and secondary somatosensory areas. Active movement, however, was associated with activation of the primary sensorimotor cortex, premotor cortex, supplementary motor area, secondary somatosensory areas, basal ganglia and ipsilateral cerebellum. As the active movement task was controlled kinematically in the same way as the passive movement task, this difference may be an effect of increased attention during an active movement task. Despite this latter controversy in the functional brain areas activated in active and passive movement, it appears at least that it is possible to obtain reproducible contralateral primary somatosensory (and motor) cortex neuronal activity from a purely passive movement task. The presence of primary motor cortex activation may be explained by initiation of muscle contraction by the cortical motor neurones during active hand flexion. However, this would not explain activation by passive hand flexion, which could be due to sensory feedback from muscle and joint receptors.

Passive movement may be useful for investigations of patients where the ability to perform adequate finger movements is impaired, if the patient is unco-operative, or for particular experimental conditions where the comparison between left versus right motor tasks is required but they are unable to move their hands independently of each other (Krams et al. 1997).

2.3.1.3 Electrical stimulation of a peripheral nerve

A number of fMRI studies have used electrical stimulation of the median nerve or fingers to stimulate the sensorimotor cortex. fMRI studies at a variety of field strengths (2 to 7 Tesla) have been performed in rats and have shown responses in the sensorimotor cortex to electrical stimulation of the fore-paw (Hyder et al. 1994; Gyngell et al. 1996; Scanley et al. 1997; Reith et al. 1998). The fMRI results in human studies are, however, divided as to the success in detecting activation. Several groups have reported distinct contralateral sensorimotor cortex activation in response to median nerve stimulation in the majority of subjects studied (Baudeweg et al. 1997; Buchert et al. 1997a; Schreiber et al. 1997; Villringer et al. 1997; Grimm et al. 1998). In a number of studies, activation was also seen in one, or all, of the bilateral SII areas, the contralateral posterior parietal cortex and the ipsilateral primary sensorimotor cortex (Korvenoja et al. 1996; Villringer et al. 1997). Several studies have also used electrical stimulation to ascertain somatotopy within the sensorimotor cortex, both in gross (whole limb) and fine (individual finger) detail (Villringer et al. 1997; Kurth et al. 1998). It has been reported that a smaller number of voxels are activated compared to those with active motor tasks (Cao et al. 1993; Tintera et al. 1994; Baudeweg et al. 1997), and that they have a low signal intensity (Cao et al. 1993; Peters et al. 1996) and may be attributed mainly to veins (Tintera et al. 1994; Hara et al. 1997). Other groups have attempted to use the technique, but have been unsuccessful in recording visible fMRI activation (Constable et al. 1993; Puce et al. 1995; Hara et al. 1997) or found it to be poorly reproducible (Peters et al. 1996). A recent fMRI study has investigated the motor as well as sensory cortex activation on stimulation of the median nerve (Spiegel et al. 1999). There is a wealth of literature providing evidence for precentral generators of early SEP components in response to electrical median nerve stimulation (for example Deiber et al. 1986, for review see Section 4.1.2.1 of Chapter 4). In accordance with this, fMRI studies have indicated that the primary motor cortex in addition to the primary sensory cortex can be activated by median nerve stimulation at frequencies normally used for SEP recording (specifically 0.5-2Hz) and in the absence of a motor command (Spiegel et al. 1999). Stimulation of the median nerve and a sequential finger opposition

movement caused a peak signal increase in the same areas of the contralateral primary sensory and motor cortices, the size of the activation being significantly larger in S1 for electrical stimulation and in M1 for active movement tasks.

The electrical stimuli in the studies discussed in this literature review were delivered over a range of frequencies between 1 and 30Hz. Puce et al. (1995) suggested that the reason for the inconsistent activation seen in their results could be that a more continuous stimulus (such as brushing of the skin or stimuli at or above 15Hz) is required to generate a larger local blood flow increase, and so a more reliable fMRI signal. In contrast, Davis et al. (1995) reported only weak activation of SI using electrical median nerve stimulation at 50Hz unless the stimulation intensity reached a painful level. Subsequent studies have shown that intermittent stimuli, even at frequencies as low as 1Hz, may still produce reproducible fMRI activation (Tintera et al. 1994). Interestingly, Tintera et al. (1994) also showed that in two volunteers in whom a high frequency stimulation (100Hz) was used, there was no activation visible in the contralateral sensorimotor cortex. In addition, one recent study has reported sensorimotor cortex activation in response to lower stimulus frequencies of the median nerve between 0.5 and 2Hz (Spiegel et al. 1999). Several imaging studies have directly examined the dependence of activation on stimulus frequency in response to electrical stimulation. Ibanez et al. (1995), in a PET study in humans, demonstrated a peak intensity of activation in the range of 4Hz using electrical stimulation of the median nerve, reaching a plateau at higher frequencies. This plateau around 4Hz frequency is a finding that has since been replicated with fMRI in both rats (Gyngell et al. 1996; Scanley et al. 1997; Reith et al. 1998) and humans (Kurth et al. 1998; Spiegel et al. 1999). A possible interpretation of a plateau of activation at higher frequencies is that at low stimulation rates the neurones can respond to each stimulus, whilst at higher rates the response is progressively occluded due to insufficient recovery time between stimuli (Gyngell et al. 1996). Alternatively, there may be a maximum limitation on rCBF at a particular frequency and in a particular cortical area, and at this critical point there is a loss of the linear relationship between neuronal firing rate and the rCBF (Ibanez et al. 1995). This latter theory has been supported by PET studies at high continuous vibratory stimuli (Fox et al. 1987; Temple & Perlmutter, 1992) and in studies showing SEP amplitude decreases between 0.2-4Hz frequencies, whereas the rCBF increases in a linear fashion (Pratt et al. 1980; Garcia Larrea et al. 1992). In studies in which the methodology was described, stimuli were delivered at similar intensities, and so differences in stimulus intensity cannot be responsible for the variable results between studies (all intensities were delivered above sensory threshold and most at or above that needed to induce a thumb twitch). There appears to be no obvious single reason, either in the experimental

design or analysis method, for the discrepancies seen among the fMRI studies using electrical stimulation to activate the sensorimotor cortex at different frequencies.

There have been a number of studies comparing fMRI findings on electrical median nerve stimulation with magnetoencephalography (MEG) or SEP recordings under an identical stimulus paradigm. In general, strong agreement was observed between the location of cortical activation within the contralateral sensorimotor cortex and other processing areas for the different techniques, both directly (superimposition of the datasets) (Buchert et al. 1997a; Grimm et al. 1998; Schreiber et al. 1997) and indirectly by visual comparison (Korvenoja et al. 1996; Peters et al. 1996). Several studies have attempted to quantify the difference between the mean dipole location and the centre of the activation areas in fMRI, reporting discrepancies of 2.6mm (Grimm et al. 1998), 2 to 8mm (Buchert et al. 1997a), and between 3 and 10mm (Schreiber et al. 1997). The correlation of two such different techniques, one measuring the haemodynamic responses of the brain to the stimulus and the other measuring the electromagnetic responses, may provide confidence in the interpretation of such converging information.

These data on the whole support the use of electrical stimulation as a technique that is appropriate for use with fMRI. As with passive movement, its use would be particularly significant in circumstances where a patient's ability to perform adequate finger movements is impaired, or when the patient is unco-operative (as may be the case, for example, in children). Other advantages of electrical stimulation include the precise timing and reproducible application of the stimulus. Also it is a well characterised stimulus with known effects as determined from MEG and somatosensory evoked potential (SEP) recordings, and provides the possibility of correlating activated areas with results from other techniques such as SEP and MEG. It can also be adjusted to the individual's perception.

2.3.2 The effect of handedness on fMRI activations

Many studies have involved right-handed subjects due to their abundance (approximately 90% of humans are right-handed (Ellis et al. 1988)), and more clearly understood hemispheric functional asymmetry (predominantly left hemisphere dominance, for example Geschwind & Levitsky, 1968; Rasmussen & Milner, 1977). However, the cortical representation of function in left-handers has received less attention in brain mapping studies. It should be noted that approximately 70% of left handed subjects still have left hemisphere dominance (Rasmussen & Milner, 1977).

Despite the extensive fMRI and PET literature on motor cortical activation, there have been few studies comparing the cortical changes during left and right hand activation, or in subjects of differing handedness, in particular with relation to hemispheric asymmetry. Determining cortical maps from functional sensorimotor stimulation studies in normal volunteers of left and right handedness will allow the interpretation of activation patterns in a similar spectrum of patients with brain disease that potentially disrupts the normal sensory and/or motor cortical systems. For example, ipsilateral cortical activation has been demonstrated in a number of studies in left and right handed volunteers (see below), which supports the anatomical evidence for ipsilateral motor pathways. Regardless of individual handedness, left hemispheric lesions have been shown to result in more pronounced motor deficits than those resulting from right hemispheric lesions, in particular controlling the initial execution of aiming movements and changes in limb or articulatory posture (Haaland & Harrington, 1989, 1994). In addition, lesions to the rolandic region or internal capsule produce contralateral deficits but differing deficits on ipsilateral function, depending on the side of the lesion and the type of task. For example, left hemispheric lesions result in motor dysfunction (controlling the initial execution of movement) in the ipsilateral (left) hand, whereas lesions in the right hemisphere leave the ipsilateral (right) motor function relatively unaffected (Haaland & Harrington, 1989). These studies suggest a susceptibility within the left hemisphere for the presence and/or functional expression of ipsilateral cortical connections.

The presence or absence of ipsilateral activation may not only depend on the subject's handedness, but also on the complexity of the task performed (see Section 2.3.1.1). In fMRI, PET, MEG and TMS studies, complex movements such as sequential tapping of the fingers in a predetermined fixed order or unnatural 'individuated' finger movements have been shown to result in greater ipsilateral primary motor cortex activation compared to simple uncued movements (Hari et al. 1993; Rao et al. 1993; Shibasaki et al. 1993; Atlas et al. 1996; Chen et al. 1997b). Although such effects should therefore be considered when interpreting functional imaging results, as the studies below indicate, the effects of handedness can still be investigated providing the same task is performed by both hands. One early fMRI study by Kim et al. (1993b) demonstrated that the right motor cortex is activated mostly during contralateral finger movements in both right-handed and left-handed individuals, whereas the left motor cortex is activated substantially during ipsilateral movements in left-handed subjects and even more so in right-handed subjects (i.e. left hand movement resulted in less asymmetry of cortical activation than right hand movement in both left- and right-handed subjects). This involvement of the left motor cortex in ipsilateral hand movements has been linked to the

results of lesion studies mentioned in the previous paragraph, demonstrating functional deficits produced by left but not right hemispheric lesions on the performance of the ipsilateral hand. It is clear that the patterns of cortical activity in left-handed and right-handed subjects are not mirror images of each other. In another fMRI study by Kim et al. (1993a), oblique slices through the right hemisphere were taken in right-handed normal subjects and ipsilateral (right) hand movement produced an area of activation (number of activated pixels) which was 20 times smaller than that observed with contralateral (left) hand movements. The intensity of activation was 2.3 times greater in the contralateral than the ipsilateral task. In contrast, the study showed that, in one ambidextrous volunteer, the area of ipsilateral activation was only two times smaller than the contralateral activation. All volunteers in the study carried out the same motor task of finger to thumb opposition. In agreement with Kim et al. (1993a&b), Jancke et al. (1998) also demonstrated greater activation in the right hemisphere on left hand movement compared to the level of activation in the left hemisphere on right-hand movement; however, unlike Kim et al. (1993b), they did not show activation in the ipsilateral hemisphere with movement of either hand. One reason for the inconsistencies in showing ipsilateral activated regions may be a difference in thresholding the activation maps (Jancke et al. 1998). Other fMRI studies have shown ipsilateral activation in right-handed normal subjects, in particular when moving their non-dominant (left) hand during a simple motor task of hand 'spreading' (Falk et al. 1997), or a finger to thumb opposition task (Li et al. 1996; Dassonville et al. 1997; Mattay et al. 1997; Singh et al. 1998a&b). This ipsilateral activation was found in the precentral region (Singh et al. 1998a&b). In addition, bilateral activation has been demonstrated in the primary motor cortices with simple and more complex movements of both hands in subjects who are left-handed or ambidextrous, compared to unilateral activation with dominant hand movement in right-handed subjects (Dassonville et al. 1997). Such bilateral activation may be less significant than unilateral activation (Berkelbach van der Sprenkel et al. 1999). In addition, other studies with right-handed subjects have reported no difference between complex finger to thumb opposition motor studies involving the left and right hand with fMRI (Roth et al. 1996), both sides of the body inducing contra- and ipsilateral activation in the primary motor cortex. One study has reported no consistent ipsilateral activation in right-handed volunteers performing what they describe as a simple sensorimotor hand task of unilateral middle finger tapping with either hand (Boecker et al. 1994). The diversity in the results from these studies does not appear to be dependent on the complexity of the motor task.

It is clear from the literature reviewed above that there is considerable controversy regarding the pattern of brain activation on movement of the dominant and non-dominant

hand in normal subjects. More studies are needed in this area, particularly in left-handed and ambidextrous volunteers, to fully understand the role of ipsilateral brain activation in subserving normal hand function. Handedness must be taken into account when investigating patients with brain damage affecting the sensorimotor systems, particularly if the issue of cortical reorganisation of function is being addressed (see Chapter 6).

Chapter 3: Functional magnetic resonance imaging - methodology

3.1 Introduction

Many different methods for acquiring and post-processing of fMRI data have been adopted in different laboratories. In this chapter, a description is given of the fMRI methodology used for the work reported in this thesis. The post-processing methodology is discussed first, since this in turn influences the optimal acquisition method. The latter is dependent on a number of factors, including the sequence to be used and the particular stimulus paradigm chosen, and these issues are addressed in Section 3.3. Finally, in order to establish the reliability of the chosen methods, a reproducibility study is described at the end of the chapter.

3.2 Post-processing and analysis of fMRI data

A number of the initial fMRI studies were analysed by averaging (on a voxel to voxel basis) the signal intensities of all the images in each condition and subtracting the mean task image from the mean image at rest (for example Connelly et al. 1993). While this simple approach allowed the detection of large changes in image signal intensity, it was clear that the method was less effective in detecting more subtle changes and did not permit statistical evaluation. Consequently, many groups have developed and optimised more sophisticated methods for the post-processing of their fMRI data (Corbetta et al. 1991; Bandettini et al. 1993; Frahm, 1994; Gulyas & Roland, 1994; Russell, 1994; Baumgartner et al. 1995; Kwong, 1995; Zarahn et al. 1997). Many methods follow similar steps to those performed with Statistical Parameter Mapping (SPM; Wellcome Department of Cognitive Neurology), which is the method used in this thesis (Friston et al. 1994a, 1995c). However, minor variations in methods may lead to differences in the detection and observed pattern of cerebral activation.

In this section two post-processing methods are outlined, SPM and a percentage signal change algorithm.

3.2.1 Statistical Parametric Mapping

Statistical Parametric Mapping refers to the construction of spatially extended statistical processes, or maps, to directly test a hypothesis. An outline of the steps involved in SPM analysis of functional data is shown in Figure 3.1.

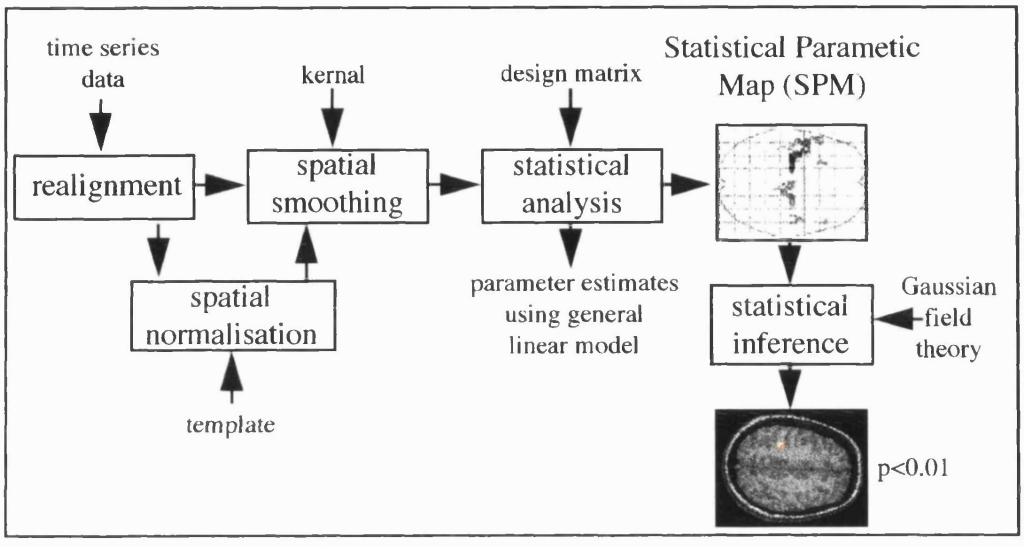


Figure 3.1: Summary of SPM fMRI post-processing analysis. See text for a description of each of the stages in the analysis (reproduced from Frackowiak et al. 1997).

Each of the steps involved in the analysis of fMRI data using SPM is described below.

3.2.1.1 Realignment

Movement-related variance in the fMRI time-courses represents one of the most serious confounds of analysis. For voxel-based statistical analysis (such as in SPM) it is imperative that all of the image data are in the same anatomical space. In addition, the removal (or at least the reduction) of motion artefacts increases the sensitivity of the subsequent statistical analysis. MR data can be brought into a standard space by a realignment algorithm, a principle developed by a number of MRI groups using different methods (Woods et al. 1992; Risinger et al. 1994; Strother et al. 1994; Biswal & Hyde, 1995a; Hill et al. 1995; Kaasam & Wood, 1995; Mock et al. 1995; Kiebel et al. 1997 Wanschura et al. 1999). In SPM, this procedure is carried out in two stages (Friston et al. 1996, 1995a). First the parameter values are determined for the rigid-body transformation between the image and a chosen reference image. As a general rule, images are realigned to the reference image acquired closest in time to the high resolution

anatomical image for more accurate superimposition and localisation of functional regions (in this thesis this is the first EPI image in the dataset). Realigned images are then transformed by resampling according to the pre-determined parameters, and each voxel in the transformed image is mapped on to the corresponding intensity in the original image.

3.2.1.2 Spatial normalisation

Intersubject averaging allows comparisons between groups of subjects. In this averaging, the datasets for each individual must be spatially transformed so that they conform to a standard brain (Friston et al. 1995a). Normalisation was not performed in this thesis as fMRI allows the investigation of individual data sets. This advantage of fMRI relies on the focal changes in haemoglobin between the rest and task states generally being large enough for single subject analysis to be used, enabling patients with different brain lesions and pathology to be investigated individually. In addition, due to the spatial normalisation requiring conformation to a standard brain, data from patients with large brain lesions (such as patients following hemispherectomy surgery) could not be normalised to such a standard template due to the large mis-registration between voxels on the hemispherectomised side and the standard brain.

3.2.1.3 Spatial smoothing

The process of spatial smoothing has a number of important advantages (Frackowiak et al. 1997; Friston, 1997). Firstly, it generally increases the signal relative to noise, based on the principle that haemodynamic changes are likely to be expressed over several millimetres, whereas random noise usually has higher spatial frequencies. Secondly, spatially smoothing using a Gaussian kernel of a specified width (as in SPM) conforms the data more closely to a Gaussian field model. This is important if one wants to use the theory of Gaussian fields to make statistical inferences about the resulting regionally specific effects after statistical analysis (see below). Finally, smoothing the data reduces the effects of individual differences so enabling, as in PET, the assessment of homologous functional anatomy in the brain in groups of patients. Using SPM, the data were smoothed isotropically so that the full width half maximum (FWHM) is approximately 3 times the voxel size in all three orientations x, y and z.

3.2.1.4 Statistical analysis

As described previously, many fMRI experimental designs are based on the experimenter exposing the subject to a regular periodic stimulus with the aim of detecting a related periodic pattern in the fMRI time series recorded from cortical regions involved in processing the stimulus input. Two general questions concerned with the data analysis arise from such studies: i) what is the best way to measure the temporal changes in the fMRI signal related to the stimulus? and ii) how should we decide whether any such measured change is significant or not? As yet, no consensus has been achieved regarding the optimal statistical methods for detecting focal brain activations with fMRI. Popular methods include statistical parametric mapping (Friston et al. 1995b, see below), nonparametric mapping (Solomon et al. 1996), principal component analysis (Khosla et al. 1996), receiver operating curve analysis (Le & Hu, 1997), Student's t-test (Ardekani & Kanno, 1998), fuzzy clustering analysis (Baumgartner et al. 1997b), independent component analysis (McKeown et al. 1998), and the Kolmogorov-Smirnov statistic (Aguirre et al. 1998). Because the diverse tests currently in use vary substantially in statistical power, the sensitivity and specificity of fMRI are strongly affected by the choice of the specific post-processing methodology employed (Crawley et al. 1995; Lange et al. 1995).

Statistical parametric mapping addresses the significance of localised effects in the brain in response to a stimulus. This is an approach that is based on the functional segregation of the brain and can be used to characterise physiology in terms of these localised responses. Functional segregation refers to cells with common functional properties that are grouped together and are determined by the cortical connectivity within the tissue (Zeki, 1990). This functional segregation may also be an anatomical one if a given cortical area shares a common responsiveness to, say, a motor or cognitive stimulus. This is the basis of functional brain mapping and the model upon which a search for localised functional effects is based (Friston et al. 1995d). It achieves this characterisation by treating each voxel separately (i.e. it is a univariate approach) and by performing voxel-wise statistical analysis so creating an image of a statistic or 'significance'. This is called the Statistical Parametric Map, or SPM (first conceptualised by Friston et al. 1990).

Statistical parametric mapping as a concept refers to the construction of spatially extended statistical processes to test pre-specified hypotheses about stimulus effects and their corresponding cortical regions (Bandettini et al. 1993; Friston et al. 1993; Friston et al. 1994b; Holmes & Friston, 1997, for review see Worsley et al. 1992; Friston,

1995). The resulting SPMs are images with voxel values that are, under the null hypothesis, distributed according to the Gaussian field theorem (Adler, 1981; Friston et al. 1991; Worsley, 1994; Friston et al. 1995c). Unlikely regional excursions of the SPM (i.e. under the null hypothesis, regions that are unlikely to be due to chance) are interpreted as 'regionally specific effects' (i.e. effects that reflect the difference between two sets of images). The underlying principle of SPM analysis is based on an equation that relates what one observes (a random variable), to what one expects to see. This is achieved by expressing the observations (the response variable such as rCBF) as a linear combination of expected components (explanatory variables) with the addition of some independent residual error. This is classically called the general linear model (Friston et al. 1995c). The general linear model is employed to perform the appropriate univariate test (expressed as an F or t value) at each and every voxel simultaneously with different parameters for each voxel (Friston et al. 1990, 1991; Worsley et al. 1992).

In SPM, the experimental design and the model used to test for specific neurophysiological responses are embodied in a mathematical structure called the design matrix. Within the design matrix, each of the conditions within a fitted waveform represent a stimulus epoch (such as alternating between rest and task), to describe the acquisition paradigm. This waveform or response function for each epoch of scans constitutes a particular specified condition, and represents a transient response to the epoch onset lasting the duration of that epoch (Bandettini et al. 1993; Friston et al. 1994a, 1995b; Worsley & Friston, 1995). The waveform adopted for the paradigm used in this thesis is called the delayed box-car. It is a fixed response function characterised by a square waveform. The waveform is however delayed by 6 seconds which allows the box-car waveform to fit the physiological response function more accurately due to the haemodynamic response delay at the onset and cessation of a condition epoch (rest or task) (Bandettini et al. 1993). Also in the design matrix, global normalisation is applied to account for whole brain intensity fluctuations between scans due to any receiver gain and transmitter power changes, and a series of high pass filters are applied to remove or model low frequency variations in signal due to artefacts such as aliased cardiac and respiratory biorhythms. Within the analysis, the data are also temporally smoothed using a Gaussian filter that approximates the haemodynamic response function (Friston et al. 1995b).

The contribution of each effect to the observed physiological responses is estimated using the general linear model and standard least squares analysis (a method used to estimate parameters that 'best fit' the data). The estimated contributions are known as 'parameter estimates' and, for the experiments performed in this thesis, can be thought

of simply as the mean brain activity associated with a particular condition, either task or rest. Regionally specific effects are framed in terms of the differences among these parameter estimates (e.g. an activation effect when subtracting the rest estimate from the task) and are specified using 'contrasts'. For each contrast (or differences in parameter estimates), a t statistic is computed for each and every voxel to form a SPM(t). For convenience, the SPM(t) is transformed to give a Gaussian field distribution at each point, or SPM(Z). By specifying different contrasts one can test for a variety of effects and interactions between parameter estimates, for example between the task and rest states, or between two different tasks. Other, more complex, design matrices and experimental paradigms (consisting, for example, of more than two parameter estimates) have been extensively described elsewhere (for example Friston, 1998).

3.2.1.5 Statistical inferences

Images contain a great number of voxels so that the SPM's are not directly interpretable. An essential step is to find a way to correct for the multiple comparison problem. A difficulty with this correction lies in the non-independence of voxel intensities due to both the initial resolution of images and to postprocessing, especially smoothing. The non-independence of voxels cannot be treated with 'Bonferroni' procedures that treat voxels as if they were independent because they are much too stringent and would wipe out statistically reliable activation signals from the results.

In this section, the use of SPM is described for making statistical inferences about specific regional effects. The exploration and characterisation of the responses observed using the fitted responses (parameter estimates) is based on both spatial extent and peak intensity thresholds (Friston et al. 1994b). If one knew where to look beforehand, then this inference could be based on the value of the statistic (Z values in the SPM(Z)) without correction for multiple non-independent comparisons. If however, as mentioned above, one does not predict an anatomical site a priori, then a correction for the multiple non-independent comparisons that are performed in the analysis has to be made. These corrections are usually made using distribution approximations from the theory of Gaussian fields. The Gaussian random field theory is used to make inferences as the data are not independent, by virtue of smoothness in the originally acquired data, and allows the computation of a corrected p value for multiple comparisons. The corrected p-value protects against the presence of false positives within the analysis.

SPMs are displayed at a specific 'height' threshold (level of statistical significance) combined with an 'extent' threshold (size of a 'cluster' of voxels that is considered significant) from the Gaussian random field theory (Poline et al. 1997; Frackowiak et al. 1996; Roland & Guylas, 1996). This bivariate test has the advantage of requiring fewer computations in addition to preserving the spatial resolution of large signals. The difficult decision is the parameter settings in the inference, i.e. the thresholds for spatial extent and peak height. Although the analysis does not occur at the voxel level, the interpretation of the results will clearly be different depending on the chosen threshold (the higher the threshold, the greater the chance that most of the voxels in the cluster are part of a real signal change associated with the stimulus). Using the theory of Gaussian random fields, the spatial distribution of the Z statistic in the SPM under the null hypothesis may be determined and thus significances, corrected or uncorrected for multiple comparisons, may be assigned to voxels, clusters, and sets of voxels.

3.2.2 Analysis of percentage signal change

The output p-values and Z-scores from statistical fMRI maps of activated brain regions are not necessarily suitable to be used as comparative statistical values between experiments. This is because Z-scores in the datasets are dependent on random effects within an experiment (for example due to different contributions of motion artefact) and this cannot be assumed to be the same in every experiment. An alternative parameter is therefore necessary if the data are to be used to make valid conclusions from comparisons between experiments. Percentage signal change was chosen as the measuring parameter using a method that took into account trends within the datasets and the removal of spurious outlying points.

The method that was established uses the output data from the SPM package, which have been treated with high-pass temporal filtering and temporal smoothing (see Section 3.2.1.4). This ensures that data used in the percentage signal change analysis are the same as those used in the SPM output. Using an alternative display program (C. Hutton, Wellcome Department of Cognitive Neurology, London, personal communication) to that in SPM96b, the smoothed functional activation maps were superimposed on to axial base images at a user-specified threshold (usually with a height threshold of $p<0.01$, extent threshold $p<0.05$). Activated regions (clusters) were then selected from the region of the contralateral primary sensorimotor cortex. The time course of adjusted signal intensity averaged over voxels in the cluster was then displayed over the 120 images and converted to percentage signal change about a

calculated mean over the time course (Figure 3.2). The time course should display fluctuations in signal intensity which correspond to the rest and task states (delayed by 5-10 seconds due to the haemodynamic response function).

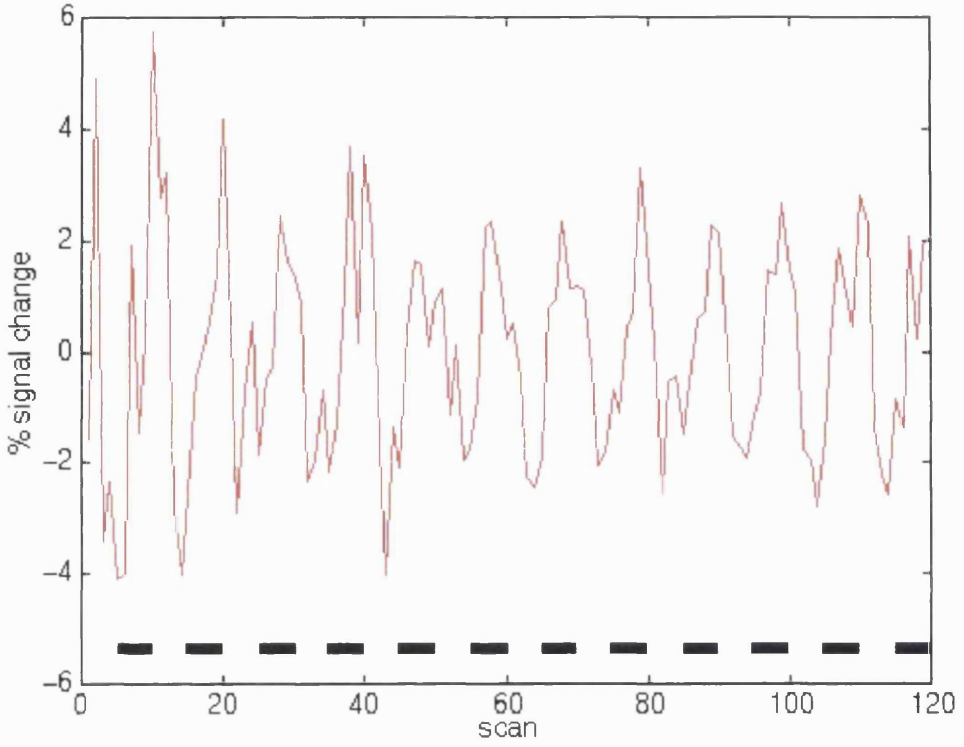


Figure 3.2: An example of a typical time course of percentage signal change against scan number in the contralateral sensorimotor cortex for an active hand motor task. Shaded blocks indicate periods of hand movement during the time course.

The aim was to obtain a 'difference' response time series where the response is the difference between the signal obtained during activation and the signal during the preceding resting state, the final output being expressed as a percentage signal change. Differences were calculated between the 12 adjacent rest and task epochs (omitting the first scan in each block to account for the delayed cortical haemodynamic response) and plotted as a difference time series (Figure 3.3).

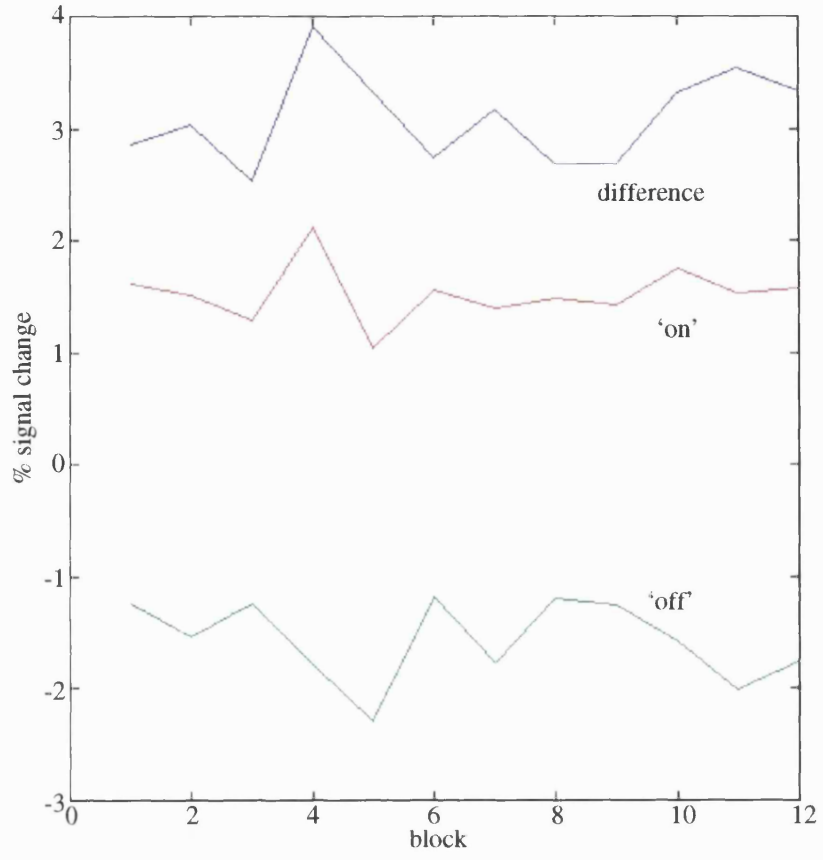


Figure 3.3: The difference values (called the response time series in blue) calculated from the 'on' (red) minus the preceding 'off' (green) blocks shown in Figure 3.2 over the whole time course.

Two considerations had to be taken into account when analysing the 'difference' response time series. Firstly, the possibility of a significant time dependence in the difference score (i.e. trends) had to be considered, which may be present in the series, for example due to habituation effects. If such time dependence is observed then it must be accommodated in the analysis and accordingly the mean could not be used in isolation as a summary parameter. Investigations were carried out, therefore, to test for the presence of time dependence in this 'difference' time series. Taking a total of 64 individual time series in turn, which were collected in a motor study using 11 volunteers, a first order polynomial fit was compared with that obtained using a quadratic (full) model for each of the time series. Quadratic polynomial regression fits were included in the analysis, because simply taking a mean of the data points may be grossly mis-representative of the true value if trends in the dataset were present (Figure 3.4). Analysis of variance (prob>F) was used to compare the models and address the possible existence of trends in the individual difference profiles. No assumption was made about the presence or absence of trends before the analysis.

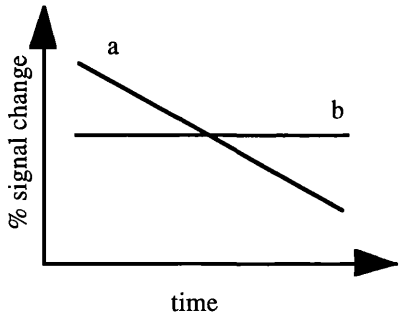


Figure 3.4: Two examples (a and b) of different timecourses in two experiments; (a) shows a downwards sloping trend in the data compared to (b). Simply taking mean values to represent each of the datasets would give identical values and no difference would be detected between the groups; however clearly they are not identical. Time dependence factors could be assessed using polynomial fits to the datasets.

The results, derived from the analysis of the 64 fMRI time series, showed greater significant differences between the first order polynomial compared to the quadratic model and the individual difference profiles. There was a significant difference between the quadratic fit and the first-order polynomials in only 4 experiments out of the total of the 64 difference score profiles. Nevertheless, it was decided to accept the quadratic polynomial regression model because is it a relatively simple approach to dealing with nuisance trends in subsequent data. The mean integrated value of the fitted polynomial curve was finally used as a summary measure of the average percentage signal change over the timecourse. This mean integrated value was used rather than the value of the regression intercept because the former is unique while the latter depends on the type of polynomial used and the x-variable transformation used (for example see Figure 3.4). In other words, while there would be a big difference in the trend/gradient between the two lines, the mean shifted value where the lines cross would show no difference. Albeit more time-consuming, the use of this method to analyse the average percentage signal change in an experiment enabled us to explore the possible existence of consistent trends in the data. In most subjects, however, there would be little difference between using a second-order and first-order fit, except that by fitting a second-order polynomial anomalous points can be identified and decisions can be made about such outliers.

The second consideration to be taken into account when analysing the 'difference' response time series is how to deal with spurious data points. It was decided to remove spurious points within the dataset if they were seen to be grossly outlying from the fitted quadratic polynomial. Other single spikes of exceedingly high or low signal change over the time course must also be accounted for, as such large artefacts may bias the final data. These spikes and corresponding difference blocks were rejected on the criterion that they occurred not only within the area of sensorimotor cortex activation, but also

within other areas of the brain and are thus likely to be artefactual rather than real local blood flow signal intensity fluctuations associated with the task.

3.3 Acquisition methodology and development of an optimal paradigm

In the following sections, the results of a number of separate experiments are discussed which together were carried out to produce an optimal paradigm for the examination of sensorimotor function in controls and in patients with brain lesions.

3.3.1 Two-dimensional versus three-dimensional EPI sequences

Much effort has been put into the development of rapid imaging techniques which can be used to follow dynamic changes in brain physiology, in particular involving the use of Echo Planar Imaging (EPI) (Mansfield, 1977; Turner et al. 1991; Stehling et al. 1991; Bandettini et al. 1992; Edelman et al. 1994; Buchert et al. 1997b; Rombouts et al. 1997; Hertz-Pannier et al. 1999). This method has the major advantage that it allows an acquisition time per image of less than 50 ms, which has been shown to be short enough to significantly reduce within-image motion artefact (Stehling et al. 1991; Turner, 1992), for review see (Bandettini & Wong, 1998). Multi-slice EPI therefore allows activated areas throughout the brain to be detected in a very short time. The major limitation to EPI, however, is the poor spatial resolution (typically around 2-3mm) compared with slower MRI techniques such as FLASH imaging (Haase et al. 1986; Connelly et al. 1993; Fellner et al. 1998).

Advances in EPI sequences for functional imaging include the development of a 3-dimensional (3-D) acquisition technique, as opposed to the commonly used 2-dimensional (2-D) multi-slice method (Guilfoyle et al. 1989; Onodera et al. 1995; Glover, 1996; Porter et al. 1997; Yang et al. 1997). 3-D EPI uses a slab-selective excitation with conventional phase encoding in the slice (z) direction (Figure 3.5), in comparison with the conventional 2-D method acquiring contiguous multi-slice images.

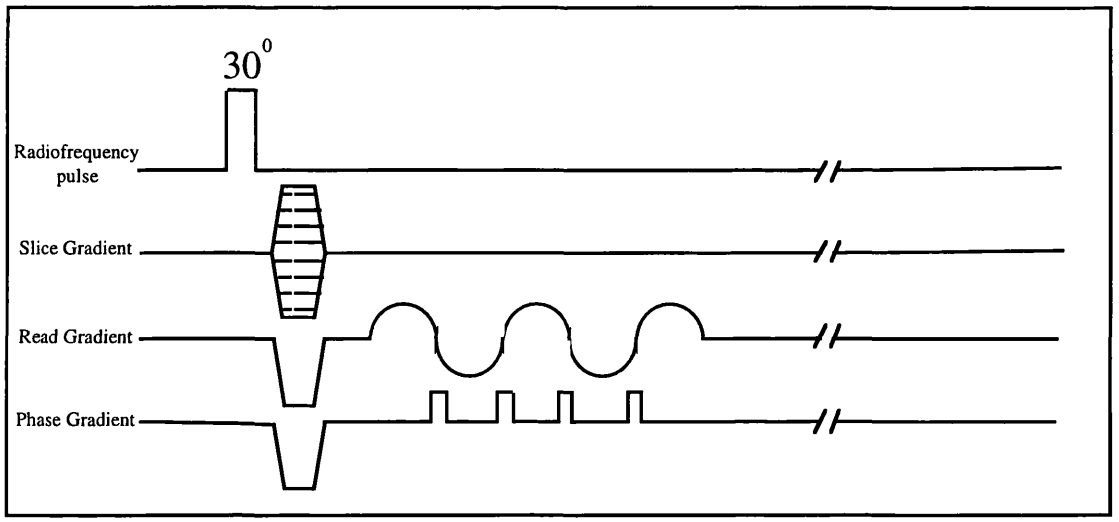


Figure 3.5: A schematic diagram outlining the 3-D EPI pulse sequence

3-D EPI allows volume images to be acquired that have the same resolution and acquisition time as 2-D EPI for the same coverage of the brain (Porter et al. 1997). The technique also has the following intrinsic advantages:

- For extensive coverage of the brain, 3-D EPI has a higher signal-to-noise ratio than 2-D EPI. This reflects the fact that, when a large number of slices is required, it is more efficient (with respect to the signal to noise ratio per unit time) to perform volume excitation in conjunction with phase-encoding the slice direction than to use multi-slice excitation as in 2-D.
- As described in the previous chapter (Section 2.2 of Chapter 2), blood flowing into a selected slice yields a higher signal intensity (because the spins are unsaturated) than static tissue. Single slice imaging methods (such as 2-D EPI) are very susceptible to these inflow effects. In 3-D EPI, the inflow effects are negligible as the blood spends sufficiently long within the slab to be subjected to a series of radiofrequency pulses similar to static tissue, and so the BOLD contrast should be dominant (Duyn et al. 1994; Frahm et al. 1994; Gao et al. 1996; for review see Kwong, 1998).
- 3-D EPI is less sensitive to the spin saturation history effects which can produce artefactual signal changes that cannot be eliminated by an image realignment technique. In addition, the images are decreased in contrast, so reducing intra-image motion artefacts due to edge effects (for example at boundaries between CSF and grey matter, or grey matter and white matter).
- The near-isotropic point spread function of 3-D EPI improves the performance of the sinc interpolation algorithm used in the image realignment procedure (see Section 3.2.1).

The objective of the study described below was to compare the performance of 2-D and 3-D EPI for acquiring fMRI maps of the whole brain.

3.3.1.1 Methods

In this study, 6 volunteers (mean age 30 years, 2 males) were scanned using both the 3-D and 2-D EPI sequences whilst carrying out the same task. The task consisted of sequential movement of the fingers to the thumb at a rate of 2Hz, cued by LED lights set inside goggles fixed on top of the head coil which were left switched on through the session. Two volunteers underwent this protocol twice to ensure reproducibility of the results.

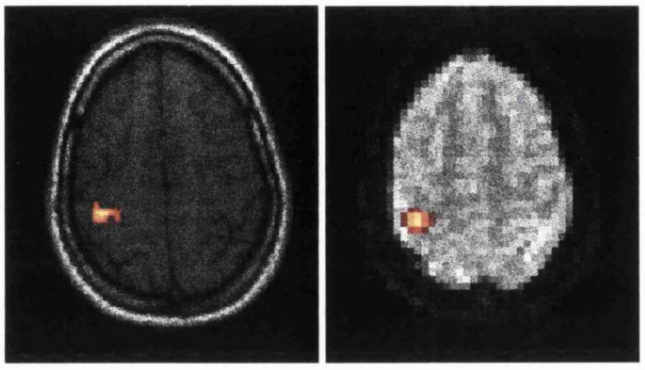
A total of 60 scans were acquired per experiment, task and rest states alternating every five scans, so that a total of 6 blocks per state were obtained. T1-weighted axial anatomical images (TR=31ms, TE=11ms, flip angle=40°, matrix size=256x256, 64 slices which were 3 mm thick, FOV=192mm) were acquired at the beginning of the session and covered an identical region to the EPI slab for localisation of significant regions of activation. Datasets acquired in the same session were analysed using SPM. Images were displayed at an uncorrected p-value threshold of $p<0.01$.

The 3D EPI sequence used in this study had a 64x64x64 image matrix with isotropic 3mm resolution, with an acquisition time of 5.6 seconds (TR=87ms, TE=40ms, Flip angle=30°). The 2D EPI sequence had a matrix size of 64x64 voxels within a slice and 64 slices (isotropic 3 mm resolution, TR=5.57s, TE=40ms, Flip angle=90°). Images were displayed at an uncorrected p-value threshold of $p<0.01$, and an extent threshold of $p<0.05$.

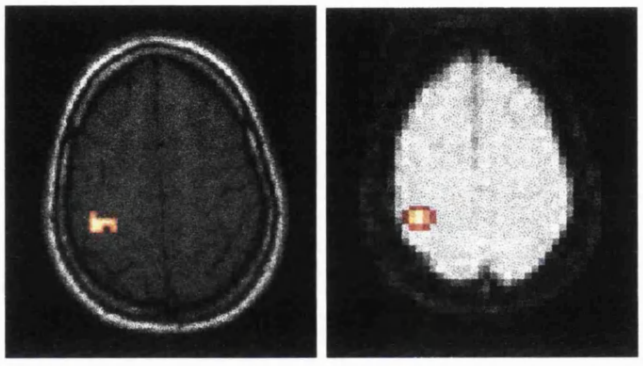
3.3.1.2 Results

Contralateral sensorimotor cortex activation to movement of the hand was seen in all volunteers using 3-D and 2-D EPI. The location of the peak region of activation was very similar using the two sequences in all of the volunteers. An example of the activations seen in one volunteer is shown in Figure 3.6. However, the activation maps on 2-D EPI showed in some instances more artefactually activated voxels both within the brain and occasionally outside of the brain (for example see Figure 3.7). In addition,

as can be seen in Figure 3.6, the 2-D EPI scans showed a higher grey/white matter contrast compared to the 3-D EPI scans, which, as mentioned above, can increase the consequences of task correlated motion.



2-dimensional EPI



3-dimensional EPI

Figure 3.6: Example of contralateral sensorimotor cortex activation in one subject using 2-D and 3-D EPI sequences. Regions of activation are superimposed on to a T1-weighted anatomical slice (left) and a corresponding EPI base image (right). 2-D EPI produces images with a greater contrast than 3-D EPI.

a)

b)

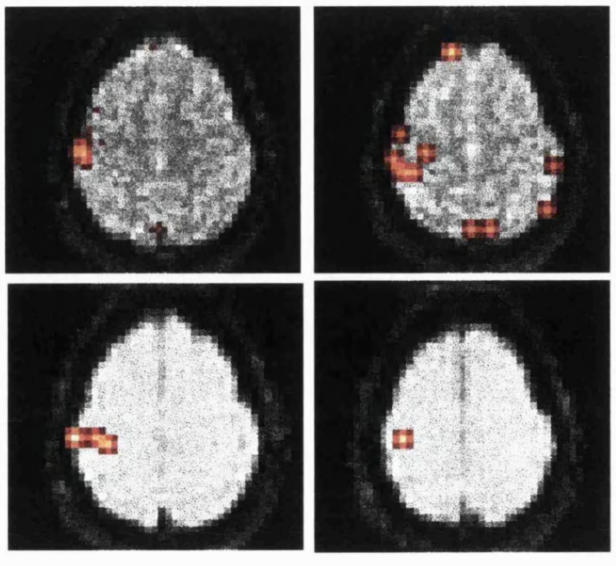


Figure 3.7: Two contiguous axial slices in one subject using 2-D (a) and 3-D (b) EPI. More artefactually activated voxels can be seen with 2-D than with 3-D EPI.

3.3.1.3 Conclusions

No visible differences between the incidence or location of fMRI activation within the sensorimotor cortex were seen using 2-D or 3-D EPI sequences in any of the 6 volunteers. As described previously, 3-D EPI has a number of intrinsic advantages over 2-D EPI. Due to these advantages, together with the fact that the activated regions observed using 3-D EPI were similar to those with 2-D EPI but with fewer artefacts in the former, 3-D EPI was used in the fMRI studies described in this thesis.

3.3.2 Fine tuning of the protocol

There is not yet an 'ideal' fMRI methodology which all groups with similar MR systems agree on. In general, fMRI groups have developed their own technique for fMRI image acquisition depending on the factors described below and the aim of the experiment in question. In this section, the results of several experiments are described which all contributed to the decision of an optimal fMRI paradigm used in subsequent investigations.

3.3.2.1 Frequency of task/rest alternations

Most fMRI groups have adopted a 'box-car' method of task and rest presentation frequencies. In its simplest form, this consists of simply alternating the two conditions (task and rest) throughout the experiment, ensuring that a similar number of task and rest images are acquired. These studies usually assume that sustained activation occurs during each cycle; however this may not be the case for all areas of the brain and so the paradigm must be carefully considered for each study. One of the major advantages of the method is that it allows non-stimulus correlated motion and signal intensity drifts (such as cardiac, respiratory and other motion artefacts) in the image data to be filtered out, as they are most likely to occur at entirely different frequencies; this increases the statistical power of the subsequent analysis (see Section 3.2.1). One debated issue using this method is the duration (and so the frequency) of the task/rest states. There are a number of points that need to be considered:

- As mentioned above, the haemodynamic response to activation takes between 5 and 8 seconds to reach a steady state. Each 3-D EPI scan (covering the whole head in

one acquisition) takes 5.6 seconds to acquire. Therefore each block must be sufficiently long for the haemodynamic changes to reach a constant level.

- Several studies have suggested that with an extended period of stimulation (from approximately 2-5 minutes after the start of the stimulus) a gradual decrease in the signal change can be seen over the period (Hathout et al. 1994; Frahm et al. 1996; Kruger et al. 1996). This has been explained either by a decrease in neuronal firing with subject habituation or fatigue effects and/or by an increase in oxidative metabolic rate over time which recouples perfusion and oxygenation consumption at a new equilibrium. Contradictory results, however, have shown no evidence of a 'vanishing' BOLD signal during sustained stimulation, strengthening the argument for using longer epoch lengths (Bandettini et al. 1995; Kollias et al. 1996; Bandettini et al. 1997; Chen et al. 1998). It has been demonstrated that this discrepancy cannot simply be ascribed to different imaging methods (Howseman et al. 1996, 1998).
- It must also be considered that the haemodynamic response function may vary across brain regions. As mentioned above, paradigms must be carefully chosen to take account of all functional cortex responses as much as possible.

One study has examined the relationship between the activation voxel number and performance time length (duration of task/rest state) during a motor paradigm (Liu et al. 1999). These authors found that performance lengths of 10, 30, and 40 secs produced similar number of activated voxels; however periods as long as 60 secs resulted in subject fatigue, caused more motion artefacts, and also resulted in fewer activated voxels. On the other hand, periods as short as 3-5 secs were easier to perform for the subjects, but produced fewer activated voxels due to less signal change.

The aim of the study described below was to compare two durations of motor task/rest states (5 scans on/off and 10 scans on/off, with a duration of 29 seconds and 58 seconds, respectively). The regions of activation and the suitability of the duration of each state are compared between the two frequencies.

3.3.2.1.1 Methods

Four volunteers participated in the study (3 males, 1 female; mean age 32 years). Two experiments were carried out to compare the fMRI activation maps associated with two task/rest durations (two frequencies), namely 5 scans (29 seconds) and 10 scans (58 seconds). These epoch lengths were chosen as they are long enough to ensure that a prolonged state of detectable activation and so an adequate signal change is reached, but

the subject would not be expected to exhibit large habituation, tiredness or boredom effects during each phase.

A total of 60 scans were acquired per experiment, using the 3-D EPI sequence described in Section 3.3.1. The same task was carried out in both experiments. The task consisted of sequential movement of each finger to the thumb with the right hand at a rate of 2Hz, cued by LED lights set inside goggles fixed on top of the head coil which were left switched on throughout the session. In addition, a T1-weighted axial anatomical scan (TR=31ms, TE=11ms, flip angle=40°, matrix size=256x256, 64 slices, FOV=192mm) was acquired at the beginning of the session, covering the same region as the EPI slab, to permit localisation of significant regions of activation. Datasets acquired in the same session were analysed together using SPM. Images were displayed at an uncorrected p-value threshold of $p<0.01$ and an extent threshold of $p<0.05$.

3.3.2.1.2 Results

All four volunteers demonstrated contralateral sensorimotor cortex fMRI activation on movement of the hand in all experiments. Examples of the results in two of the subjects are shown in Figure 3.8 and Figure 3.9. There was no visible difference in the extent or location of the sensorimotor cortex activation between the two frequencies. Practically, subjects reported they found a frequency of 5 datasets on/off easier to perform than 10 on/off as they did not feel as fatigued in their hand.

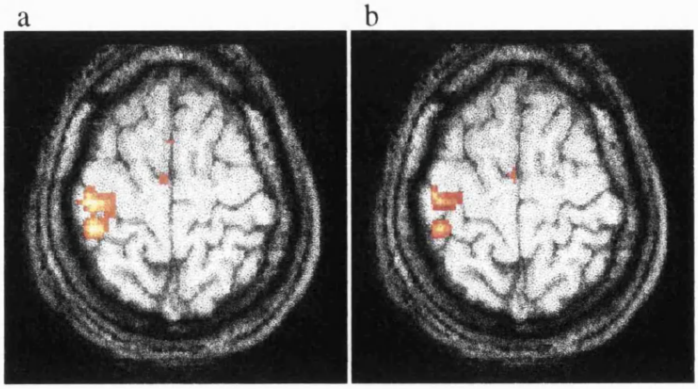


Figure 3.8: Example of contralateral sensorimotor cortex fMRI activation in one axial slice on right hand active movement in one subject acquired using a task/rest frequency of 10 scans (a) and 5 scans (b). SMA activation close to the longitudinal fissure is also seen in the images.

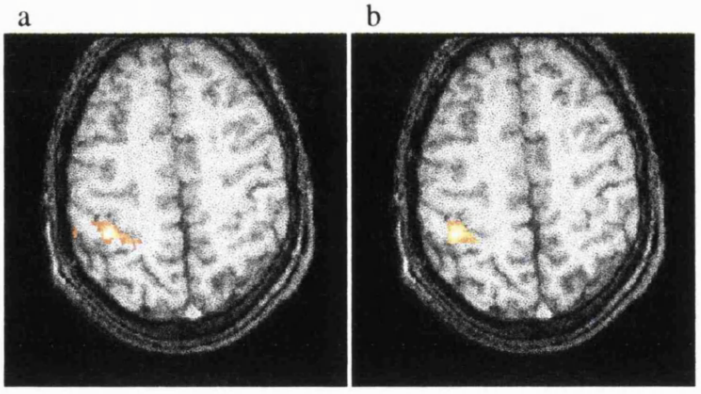


Figure 3.9: Example of contralateral sensorimotor cortex fMRI activation in one axial slice on right hand active movement in one subject acquired using a task/rest frequency of 10 scans (a) and 5 scans (b).

3.3.2.1.3 Conclusions

As described above (Section 3.3.2.1), there are several advantages for selecting as short a task/rest frequency as possible, but also one that is also long enough to ensure that data are collected within a state in which the haemodynamic changes have reached a constant level. This experiment has demonstrated that there was no consistent visible difference between sensorimotor cortex activation using two task/rest frequencies of 5 and 10 scans per epoch. Unlike the study by Liu et al. (1999), we have not shown a significant increase in motion artefacts or a decrease in activated voxels in on/off frequencies of 10 datasets compared to 5. However, the subjects did report fatigue occurring at longer performance periods, in agreement with Liu et al. (1999). For the purpose of this study, therefore it was decided that a task/rest frequency of 5 scans per epoch (29 seconds in each state) would be used for the acquisition of data in adult and child controls and children with brain disease.

3.3.2.2 Achievement of an MR 'steady state'

Using a short repetition time (TR), T_1 relaxation effects become prominent in the early measurements of a time series. If a TR is chosen such that significant saturation occurs during the time series, then a small number of dummy or pre-scans should be collected prior to those in the experiment. This will allow the establishment of a steady state in the magnetisation by the time the experiment begins, and so the signal intensities will be consistent between the early and late acquired scans in the experiment. This is

particularly important if the reference scan used in the realignment analysis is taken as the first scan in the experiment.

It is common to discard between 2-8 pre-scans before the onset of the experimental scans. It was decided that the first 5 scans should be omitted as pre-scans in this paradigm (five scans were chosen as subsequent on/off blocks were counted in blocks of five).

3.3.2.3 Total number of scans to acquire per experiment

There is a long-standing debate as to the optimal total number of scans (number of task/rest blocks) to acquire in an experiment. Several factors need to be considered:

- the greater the number of scans acquired (the larger the number of task/rest scans) the greater the signal to noise and thus the greater the probability of obtaining a significant result;
- it is preferable for the scan time to be relatively short, especially when working with patients (in particular children) and if a number of experiments need to be carried out in the same patient. Shorter scan times will reduce the overall motion artefact and fatigue as the subject becomes more uncomfortable and prone to movement at the end of the session.

From the points discussed above, it is clear that a balance must be reached to satisfy both arguments. The total examination time must be short enough to be endurable by the patient, yet provide an adequate number of task/rest epochs to be convinced that a reliable and reproducible activation map can be produced. The Siemens Vision system can acquire a maximum of 128 measurements during a single run before pausing for data processing. The duration of an experiment including all 128 images is approximately 12 minutes. It was decided that, despite the long length of an experiment, it would be most advantageous to acquire this maximum number of images, particularly when attempting to acquire data which may involve very low signal changes.

3.3.2.4 Origins of image motion artefacts

Imaging the human brain with fMRI relies on detecting small signal changes in the presence of very large baseline signals. However, changes in signal intensity can also

arise from several forms of image motion, and this represents one of the most serious confounds in fMRI studies.

The effect of motion can produce artifactually significant regions in the difference image and also reduce the signal to noise ratio (for review see Hajnal et al. 1995, 1996). There are a number of confounds which are thought to contribute to inter-image motion artefacts in fMRI. Hajnal et al. (1994) went so far as to suggest that regions of high signal change between rest and task scans could be entirely attributed to motion artefacts. It seems extremely unlikely, however, that apparent activation seen, for example, focally in the sensorimotor cortex could be solely due to movement when (a) there is no other area over the brain showing high signal (it is impossible to move only one area of cortex to produce an artefact!), and (b) the activated regions have been shown to be very reproducible between studies. fMRI artefacts have also been observed as a result of the motion of an object outside the field of view during fMRI image acquisition, presumably by distorting the magnetic field (Yetkin et al. 1996a). Physiological fluctuations in discrete cortical regions during rest have also been showed to result in 'significantly activated' pixels (Biswal et al. 1995b). Despite these findings, there is now substantial evidence from a great number of fMRI studies indicating that not all activation phenomena are explicable by artefact (for review see Weisskoff, 1995). Most fMRI groups now agree that, while acknowledging the importance of motion artefacts in the 'difference' images, it is equally important not to assign them too great a significance.

Stimulus-correlated motion and random head motion constitute sources of inter-image signal fluctuation. These artefacts result from changes in subject position within the scanner, and alter the image pixel values even when no physiological change has occurred. Unlike the physiological variables mentioned above, these problems cannot be reduced by 'snapshot' rapid-acquisition EPI. It is therefore imperative that head motion is limited as much as possible during the acquisition of a series of experimental images. There has been a great deal of effort spent on developing the optimal technique to fix the head in a firm yet comfortable position, but although most methods are effective to some degree, they do not entirely eliminate motion (see below). Improvements have also been made in post-processing spatial realignment of the images in the time series (Friston et al. 1996; refer to Section 3.2.1).

Non-invasive techniques for fixing the head in the magnet more rigidly than is normally done during clinical imaging include suction devices, custom-fit bite bars and moulded face mask restraints (for example Baudenendistel et al. 1997; Lo et al. 1996). In this

study, investigations were made into using a head mask which was moulded to the head at the beginning of each session. This mask is completely non-magnetic, consisting of a thermoplastic which is malleable at 60°C and sets to a solid state on cooling. This allows the mask to be moulded to the head whilst warm and fixed to a rigid frame at the back of the head before it sets. Once applied, the mask prevents a substantial amount of 'nodding' rotation (if moulded closely under the chin and around the top of the head), which is the motion that is hardest to eliminate using a standard MR head coil (Figure 3.10). The mask can be applied quickly and easily with no long lasting effects to the subject once removed.

a) b)

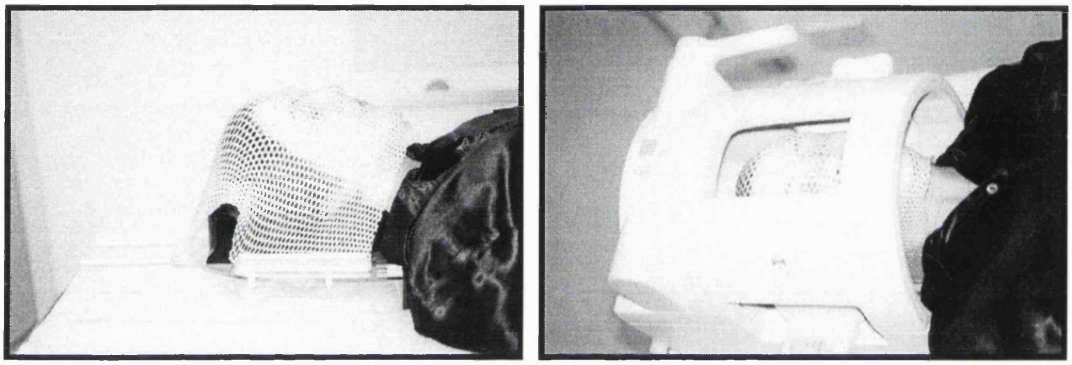


Figure 3.10: Thermoplastic head mask developed to reduce head motion. The full head mask is shown in a) and the head mask fitted into the head coil in b).

A number of disadvantages, however, became apparent after successive use of the mask. Although the mask consisted of a relatively open mesh (holes expanding up to 1cm in diameter), several subjects still felt claustrophobic, especially after about half an hour in the scanner. Most subjects reported that they preferred to do the experiment without the mask than with; however, a few said they felt more secure that they could not move their head whilst wearing it and so more able to relax. Most subjects were not completely averse to wearing the mask, even for subsequent studies. These comments made the use of the mask a possibility for use in patients, although there was an increasing probability of the patient being unco-operative (particularly with very ill patients or children).

It was decided to perform subsequent studies without the head mask. In these studies, extra time and care was taken whilst placing the subject in the scanner with the inclusion of more padding where necessary, patient comfort and relaxation being paramount. The majority of studies were successful and there appeared to be no obvious difference in the probability of obtaining a significant activation compared to results using the head mask.

Realignment parameters were comparatively small (approximately 2mm shifts in plane and 1° rotations) for most co-operative subjects (see Section 3.2.1). This finding is supported by Baudenendistel et al. (1997) who also examined the use of different head fixation techniques for fMRI and concluded that employing a vacuum pillow tightly moulded to the head did not result in significant decreases in the amount of head motion compared to standard clinical head coil fixation equipment using foam pads.

3.4 Summary of paradigm

Following all of the considerations and experiments detailed above, a paradigm for the fMRI image acquisition for the investigation of sensorimotor function was decided upon (Figure 3.11). The standard box-car method was adopted with a rest/task frequency of five scans, repeated for 12 cycles (120 scans obtained in total). In addition, 5 pre- or 'dummy' scans were acquired at the beginning of the experiment. Each scan is acquired in 5.8 seconds, the total experiment taking 12 minutes 30 seconds. Head motion was reduced using extra padding within the head coil and ensuring patient comfort. Post-processing included realignment and smoothing of the dataset, as described in Section 3.2.1, and statistical analysis using global normalisation, temporal smoothing, and a high pass filter (set at 5.8 seconds x5 scans per epoch x4 epochs = 116 seconds in the analyses in this thesis).

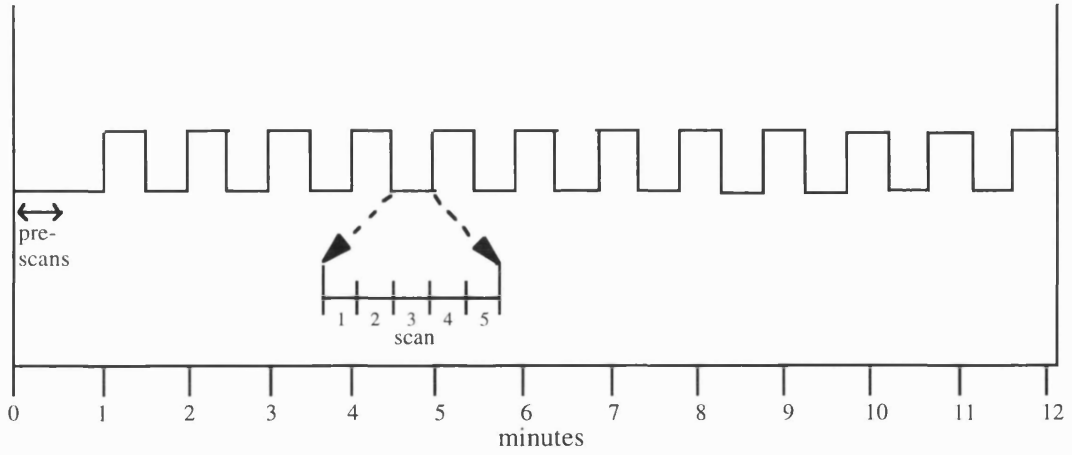


Figure 3.11: Summary of fMRI paradigm adopted.

3.5 Repeatability of sensorimotor fMRI activations between and within sessions

It is important that the reproducibility of obtaining stimulus-correlated regions of activation in fMRI is assessed in control subjects before extending the method for use in patient investigations. To date, a number of fMRI studies to assess reproducibility have been performed in normal volunteers using different stimuli and at differing field strengths and imaging techniques (Cohen et al. 1995; Mattay et al. 1996; Yetkin et al. 1996b; Baumgartner et al. 1997a; Noll et al. 1997; Jager et al. 1998; Tegeler et al. 1998; Chang et al. 1999; Cox et al. 1999; Joliot et al. 1999; McGonigle et al. 1999). All studies have demonstrated that similar regions of cortical activation (particularly in the primary cortices (Mattay et al. 1996)) are detected in terms of magnitude, location and spatial extent between experiments using identical stimuli. However, intersession differences may result in false positives when generalising the results of a single session experiment (McGonigle et al. 1999). Caution, therefore, should be maintained when comparing statistical maps with small regions of activation of low statistical significance (Jager et al. 1998).

In this study, the activated regions within the primary sensorimotor cortex of the SPM maps were investigated for reproducibility. A motor hand paradigm (finger to thumb opposition) was chosen as it has a well known physiological basis and is easily standardised both between subjects and within/between subject sessions. A common problem in the analysis of fMRI data is quantifying the statistical reliability of an estimated activation map across replications of an experiment. Several groups examining the reliability of fMRI have developed statistical models in order to define and quantify results and particular attributes of a region of activation (Cohen et al. 1995; Mattay et al. 1996; Yetkin et al. 1996b; Baumgartner et al. 1997a; Genovese et al. 1997; Cox et al. 1999). These models vary in complexity. However the most meaningful conclusions can only really be drawn from those that attempt to take into account the noise and complex spatiotemporal patterns in the activation map (such as Mattay et al. 1996; Genovese et al. 1997). In this study regional percentage signal changes in time course datasets are examined following inter-image realignment and the removal of confounds accounting for extra-signal fluctuations (Section 3.2.2).

In general, activated regions have been found to be more reproducible when comparing datasets acquired within a session, as opposed to comparisons made of datasets acquired in two separate sessions (Noll et al. 1997). Data collected between sessions are

susceptible to changes that occur within sessions plus additional sources of variation such as differences in the subject's physiological state, the equipment state, or the experimental set-up such as head location within the coil. A number of studies have demonstrated the reproducible location of a centre of activity surrounded by local spatial variability (Cohen et al. 1995; Tegeler et al. 1998); the most consistent voxels were found also to be the most significant ones (Cohen et al. 1995).

3.5.1 Methods

Eleven normal, healthy, volunteers participated in the study (2 males, 9 females; mean age 26 years). The subjects had two fMRI scans (separated by at least one day) to determine between-session variation, and in the first session they repeated the experiment twice to assess within-session variation. A hand motor task of right finger to thumb sequential opposition was performed in all cases, at a rate of 2Hz set by LED lights inside goggles fixed on top of the head coil and left switched on throughout the session. The acquisition paradigm that was used is described in Section 3.4. A T1-weighted axial anatomical scan (TR=31ms, TE=11ms, flip angle=40°, matrix size=256x256, 64 slices, FOV=192mm) was acquired at the beginning of the session and covered an identical region to the EPI slab for localisation of significant regions of activation. EPI datasets acquired in the same session were analysed together using SPM.

Percentage signal change analysis was carried out (as described in Section 3.2.2) on voxels activated above a user-specified threshold (uncorrected height threshold of $p<0.01$, extent threshold of $p<0.05$) within the region of the sensorimotor cortex contralateral to the side of the task. A maximum likelihood variance components analysis was performed using data collected from two experiments within a session and data obtained in the subsequent session. Among the advantages of this method is that it can deal with missing data points (for example if there was no activation present in the map) and performs the analysis on the variance measures directly from the dataset, rather than computing the variances via the sum of squares (as with the ANOVA test). It uses a maximisation routine to find values for variance components (specifically σ^2_{ε}, $\sigma^2_{occ(sub)}$, and σ^2_{sub}, where occ=occasion, sub=subject and ε=residual variance) which maximises the likelihood of the data.

3.5.2 Results

All 11 volunteers demonstrated contralateral sensorimotor cortex fMRI activation on active movement of the hand in both experiments within the first session. For the second session, however, the data from one subject were omitted due to motion artefact, leaving only 10 comparisons to be made with datasets acquired between sessions. In all cases, the location of sensorimotor activation was visually similar both within and between sessions (for two examples, see Figure 3.12 and Figure 3.13).

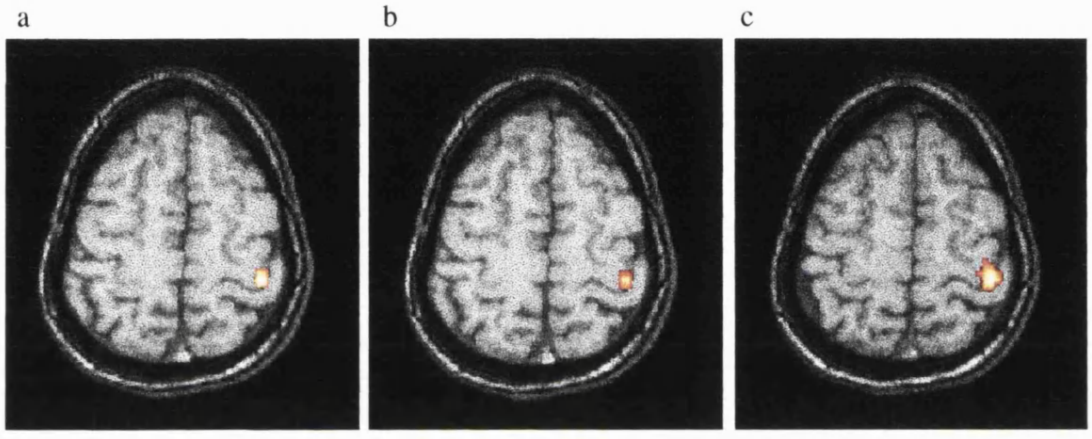


Figure 3.12: Example 1. Contralateral sensorimotor cortical activation in three runs for left active hand movement in one volunteer. Runs a and b were performed in the same session and run c performed in a subsequent session

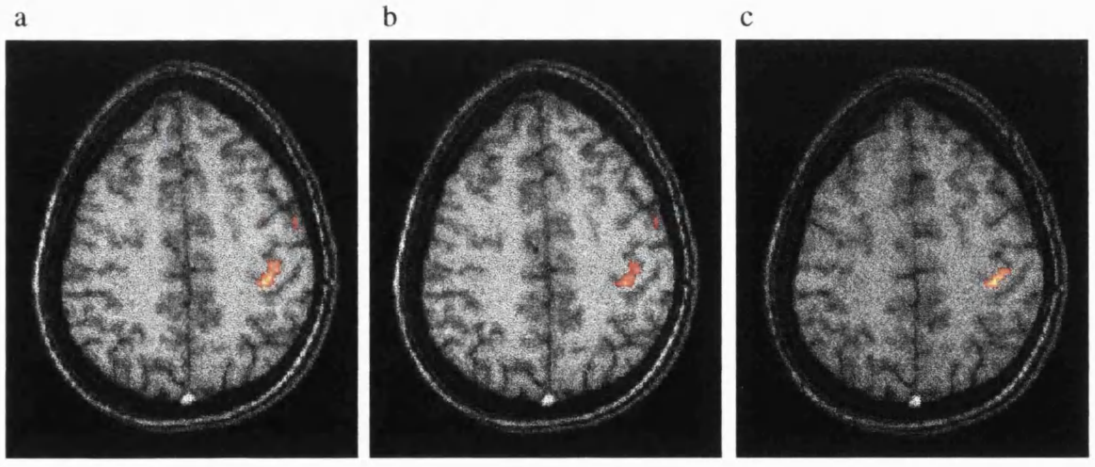


Figure 3.13: Example 2. Contralateral sensorimotor cortical activation in three runs for left active hand movement in one volunteer. Runs a and b were performed in the same session and run c performed in a subsequent session

The percentage signal change data taken from activated regions within the contralateral primary sensorimotor cortex are shown in Figure 3.14. A total of 6 percentage signal change values were collected from each of the volunteers' data, corresponding to studies

of two experiments performed within a session and one experiment in a second session, with movement of the left and right hand. These data points are displayed together for each volunteer to compare percentage signal change values over all of the experiments with the left and right hand and over all volunteers. The graph indicates a large degree of variation between the percentage signal change within each volunteer; however, there appears to be less variation in the mean percentage signal change between the volunteers. There is also no observed difference in the percentage signal change with the side of hand movement (Figure 3.14).

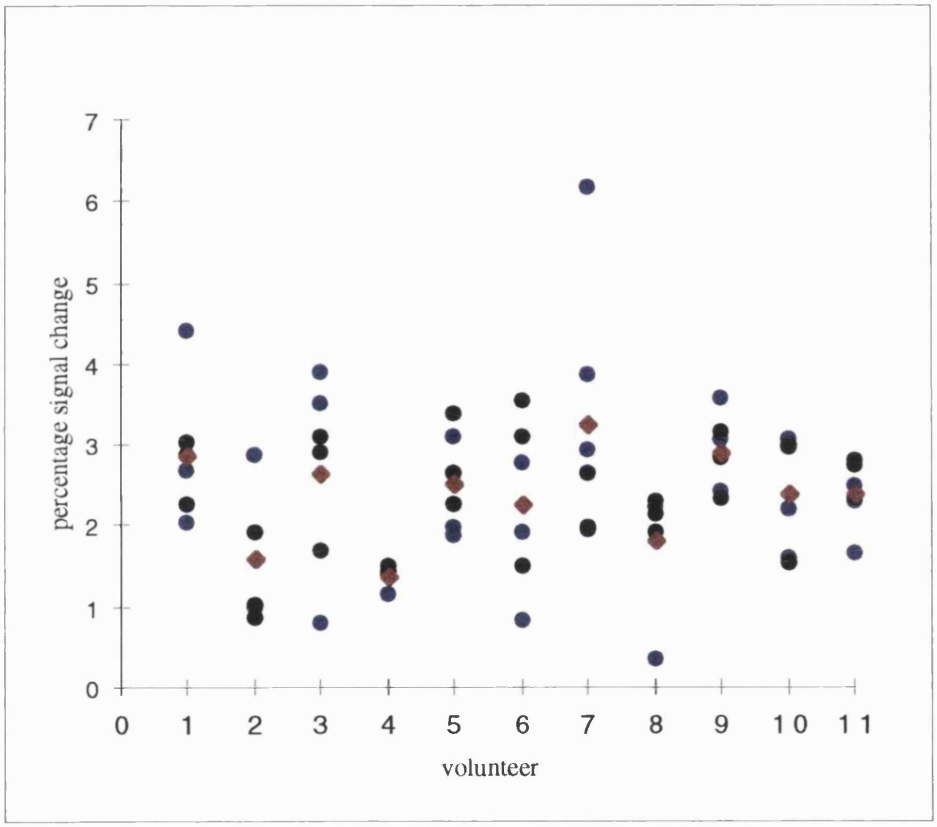


Figure 3.14: Graph to compare the percentage signal change values in repeated motor experiments (blue=right hand, black=left hand movement) carried out within and between sessions in 11 volunteers. Points in red indicate the mean percentage signal change within each volunteer over all experiments. The graph indicates a large difference in the percentage signal change values within a subject; however, the mean percentage signal change within each subject is similar across subjects.

Maximum likelihood analysis was used to obtain estimates of the variance components between subjects (sub), and occasion (occ), and residual variance was denoted ε. The model is:

$$Y_{ijk} = \mu + sub_i + occ_{j(i)} + \varepsilon_{k(ji)}$$

where i = subject, j = occasion (within subject), k = observations within occasions, and the mean is normally distributed with the parameter N(mean=0, σ^2); specifically the

distribution of the mean for each of the above parameters is given by sub = N(0, σ^2_{sub}), occ(sub) = N(0, $\sigma^2_{occ(sub)}$), and ε = N(0, σ^2_{ε}). The random occasions effect is nested within subject. The results are as follows:

- variation between subjects, $\sigma^2_{sub} = 0.063$
- variation due to occasion, $\sigma^2_{occ(sub)} = 0.459$
- residual variance (within a session and unexplained variance) $\sigma^2_e = 0.603$

In summary: $\sigma^2_e = 0.6034 > \sigma^2_{occ(sub)} = 0.459 > \sigma^2_{sub} = 0.063$

According to these results, the variance between subjects was small; however, a greater amount of variance was found between experiments on different occasions in the same subject (between sessions) and in particular in the residual variance (mainly accounting for variation within sessions, within subjects). This is visible in the data shown graphically in Figure 3.14, in which the variation within a subject can be seen to be greater than the variation between different subjects. These results were similar to those obtained from a traditional variance components analysis which obtains estimates of the variance components using the calculated mean squares together with the so-called expected mean squares.

3.5.3 Conclusions

The location of contralateral cortical sensorimotor activations can be reproducibly demonstrated using the same motor task both within a session and between sessions. In this study, we also investigated the reproducibility of the intensity of activated regions between experiments in the same and different subjects. Using the percentage signal change analysis, it appears that there is greater variation in the intensity of the significant voxels within datasets acquired in one subject than between subjects. In summary, although this study has demonstrated that it is possible to confidently compare the location of activations between experiments, there is less confidence in comparing percentage signal change values between experiments. There are two options to performing group comparisons in an fMRI study with sufficient statistical power; firstly to perform many replications, and secondly, to increase the number of subjects in the study. As the majority of this thesis concentrates on collecting data from patients, who may be less co-operative and unwilling to visit the hospital on many occasions, both of these options are impractical. As a consequence, only comparisons of the location of the regions of activation between experiments on any individual subject have been made in this thesis.

Chapter 4: Somatosensory evoked potential recording - methodology

4.1 Introduction

4.1.1 Somatosensory evoked potentials

Evoked potentials (EPs) are electrical responses elicited within the nervous system in response to sensory, motor, visual or other types of stimuli. Scalp-recorded EPs provide a non-invasive, harmless and inexpensive method to investigate brain function. They are usually recorded by electrodes which are positioned roughly equidistant from each other on the scalp. A physiological stimulus generates field potentials in the brain which originate from the spatial and temporal summation of excitatory and inhibitory post-synaptic potentials produced at the membranes of nerve cell bodies and dendrites in the cortex. These potential fluxes create currents that penetrate the cortical surface, skull and scalp thereby producing the electrical field potentials at the scalp that can be detected by recording electrodes. Differences are measured between the field potentials recorded by pairs of electrodes or by electrodes and a reference electrode (usually a relatively inactive electrode) on the scalp. EPs are displayed as a wave of activity following the stimulus. This wave consists of a series of components, each of which has a specific latency, amplitude and polarity. EPs can be generated in, and recorded from, the brain or spinal cord. The exact localisation of the generators of the EP is difficult, in part due to the complex waveforms that are produced by multiple generators. A single response to a stimulus is of low amplitude and is frequently obscured by electrical activity unrelated to the stimulus (treated as background noise). The EP is thus made visible by averaging many stimulus-response trials, so increasing the signal to noise ratio. EP recordings, although having a poor spatial resolution (approximately 1cm), have the important advantage of having high temporal resolution (of the order of less than a millisecond).

Somatosensory evoked potentials (SEPs) have long been used to investigate the somatosensory system, and now constitute an extremely reliable method for both clinical and research applications. Several types of stimuli are used to evoke SEPs, the most popular being electrical stimulation of a peripheral sensory or sensorimotor nerve, such as the median nerve at the wrist. The human median nerve contains afferent fibres

of many types, responding to different modalities of stimuli. This multiplicity of afferent fibre types is reflected by the complexity of the somatosensory cortex; different afferent fibre groups have been found to activate specific subdivisions of the primary somatosensory cortex and may give rise to different components in the SEP (see Section 4.1.2.1). The primary somatosensory cortex has now been subdivided into at least four representations, each associated with the input of a particular type of sensation or combination of sensations (refer to Section 1.4.1 of Chapter 1). It has also been suggested that the primary motor cortex is activated in SEP recordings, which is discussed in more detail in Section 4.1.2.2 below. Due to the low spatial resolution of SEPs, however, it is very difficult to distinguish between activations in each of the areas of the primary somatosensory and motor cortices (see Section 4.1.2.1).

A less commonly used method to record SEPs is vibrational (mechanical) stimulation (vSEP), which is widely reported to give smaller SEP responses than electrical SEPs (eSEP) and to be less reliable in producing an SEP response. However there are also advantages to using vibration as a method of stimulation, particularly in children, as it is less painful and easier to apply than electrical stimulation.

In the following sections a review is given on previous literature reporting electrical and vibrational SEPs, followed by a discussion of the aims of the work described in this chapter.

4.1.2 Electrical SEPs

4.1.2.1 Early latency components of the electrical cortical SEP

In this thesis, particular attention is placed on the early (or first identifiable) cortically-recorded SEP components on electrical stimulation in the normal and diseased brain. In this section, a review is provided of the previous literature on the early latency electrical cortical SEP components (between 15 and 35ms) in normal subjects. Comparisons of early and middle latency vSEP components are covered in the Discussion (Section 4.4.1).

Contradictory findings have been reported in the literature regarding the number and characteristics of the early latency components in the eSEP recorded on median nerve stimulation. Following peripheral median nerve electrical stimulation, the first cortical SEP component is called the N20 because it is a negative peak with a latency of about

20ms following the stimulus (for example Goff et al. 1977; Allison et al. 1980). Based on the findings from scalp recordings, electrocorticography and magnetoencephalography (MEG) studies, the source of the N20 is considered to be a tangential current in the posterior bank of the central sulcus 'area 3b' (Kawamura et al. 1996; Grimm et al. 1998; for review see Allison et al. 1989a; Yamada et al. 1984). The N20 is followed by several peaks, the most prominent peak being the P30 (Allison et al. 1980; Allison, 1982; Mauguiere et al. 1983; Desmedt & Bourguet, 1985). The P30 component is also thought to originate in area 3b in the postcentral gyrus (Allison et al. 1991a&b; Cedzich et al. 1996); however, there is also a suggestion that the P30 component originates in the motor cortex (Kawamura et al. 1996).

Studies have also reported a component between 22-25ms called the P22, P24 or P25, which is smaller in amplitude than the N20 or P30 components and less reproducibly observed (Desmedt & Cheron, 1980; Desmedt & Cheron, 1981; Allison et al. 1991a). The exact location of the source of the P22/P24/P25 component is controversial since it has been reported both anterior and posterior to the central sulcus (for example Mauguiere et al. 1983; Desmedt et al. 1987; Sutherling et al. 1988; Buchner et al. 1996). Several studies have suggested that this component is generated deep within the central sulcus, possibly in area 3a (Lueders et al. 1983; Jones & Power, 1984; Rossini et al. 1987; Valeriani et al. 1997).

4.1.2.2 Muscle afferent contribution to the eSEP

One of the major problems in the interpretation of the eSEP recordings following electrical stimulation of a peripheral nerve such as the median nerve is that afferent fibres serving more than one sensory or motor modality and projecting to different areas of the cortex are stimulated simultaneously. Microneurography studies have demonstrated that the human median nerve contains a multitude of large diameter sensory and motor afferent fibres responding to different forms of stimuli, such as tactile sensation, deformation of the skin, proprioception, deep pressure, vibration, and voluntary contraction (for example Vallbo et al. 1979). The literature on eSEPs has been controversial as to the contribution, if any, of the motor afferent fibres in the eSEP to median nerve stimulation. The characterisation of the afferent fibres contributing to the eSEP has particular relevance to this thesis as the technique is used to examine cortical sensory (and motor) function in patients with brain disease.

The earliest studies in animals suggested that group 1 muscle afferents do not project to the cerebral cortex (Mountcastle et al. 1952; McIntyre, 1953; Rose & Mountcastle, 1959). The first evidence that there is a muscle afferent cortical projection came from electrophysiological studies in cats and primates (Powell & Mountcastle, 1959; Oscarsson & Rosen, 1963). Burke et al. (1981, 1982) subsequently reported that there is no cutaneous component in the scalp eSEP evoked by stimulation of a mixed peripheral nerve (for example the median nerve). In fact, they suggest that the slower cutaneous volley is suppressed by a process of active inhibition by the more rapidly conducting muscle afferents. McCloskey (1978) speculated that the cutaneous afferent volley can be gated within the neuraxis by the motor afferent projection, and so makes little or no contribution to the cerebral potential. Gandevia et al. (1984) went on to support these findings, demonstrating that pure muscle afferent fibres gave rise to cerebral potentials which, in terms of latency and distribution, resembled the median nerve potential more closely than did the response to stimulation of a single cutaneous fascicle. The authors concluded that muscle afferent rather than cutaneous fibres contribute to the median nerve cortical eSEP. Further studies by the same group have reinforced these findings (Gandevia & Burke, 1988; for review see Burke & Gandevia, 1986). Additional evidence has accumulated using a variety of other stimuli such as muscle stretch (Starr et al. 1981; Cohen et al. 1985), mechanical taps (Pratt et al. 1979a; Kakigi & Shibasaki, 1984), finger movement (Desmedt & Ozaki, 1991) and air puffs (Hashimoto, 1987). This is also consistent with the view that afferents from muscle contribute to proprioception (Eklund, 1972; Goodwin et al. 1972; Gandevia & McCloskey, 1976; for review see McCloskey, 1978).

Contrary evidence that the median nerve eSEP is more likely to be dominated by the much more massive cutaneous projection (muscle afferents account for only 6% of the cross-sectional area of the nerve (Sunderland & Bedbrook, 1949)). Their finding was subsequently supported by Halonen et al. (1988) who showed that the motor branches of the median and radial nerves produced poorly defined low-amplitude cortical responses or no consistent responses at all in contrast to the cutaneous branches of purely cutaneous nerves and mixed sensorimotor nerve stimulation which were well-defined and of large amplitude. A further study by Kunesch et al. (1995) using eSEP recordings found that cutaneous fibres evoked cortical responses in 86% of the median nerve fibres stimulated while muscle nerve fibres elicited responses in only 20%. They suggested that with surface and needle scalp electrodes, cortical responses to stimulation of muscle afferents can only rarely be obtained.

The greatest limitation to SEPs is poor spatial resolution (approximately 1cm), which may not be great enough to resolve the different projection sites of the muscle and cutaneous afferents. Techniques with better spatial resolution, such as fMRI, may prove to be more useful in answering such questions and distinguishing between close functional areas of the brain. A small number of studies using high spatial resolution techniques have been carried out. However, at present they are also divided as to the contribution of muscle afferent projections to the primary motor cortex with electrical stimulation of the median nerve. One recent fMRI study was performed using median nerve electrical stimulation (Spiegel et al. 1999). A significant fMRI signal increase was observed in the contralateral primary sensory and motor cortices, and it was concluded that there is an afferent input to the motor cortex. In addition, an MEG study using median nerve stimulation allocated the N20 to the sensory cortex; however the P30 was allocated to the motor cortex (Kawamura et al. 1996). In contrast, one PET study using median nerve stimulation reported only activation in the primary sensory cortex (Ibanez et al. 1995). It is clear from the unresolved controversy in the literature that further investigations into sensory and motor function using median nerve SEP recordings are necessary. In particular, data from patients with gross or specific sensory or motor deficits should be interpreted with caution and the contribution of a motor fibre input should be considered.

4.1.3 Mechanical SEPs

An alternative approach has been the study of SEPs in response to mechanical stimulation of the body surface, either as discrete 'taps' or vibratory stimuli (for example Woolsey & Erickson, 1950; Pratt et al. 1979b; Ishiko et al. 1980; Kakigi & Shibasaki, 1984; Onofrj et al. 1990). An advantage of mechanical stimulation over electrical stimulation is that mechanical stimulation is similar to a more 'natural' or 'physiological' stimulus such as touch or pressure, and in addition it causes less discomfort to the subject (Kakigi & Shibasaki, 1984; Hyvarinen et al. 1980). Because of this, many groups feel it is a more appropriate way of examining the sensory nervous system than electrical stimulation (Pratt & Starr, 1981; Schieppati & Ducati, 1984; Hashimoto et al. 1989; McLaughlin & Kelly, 1993; Caruso et al. 1993). Despite this, however, the technique is hampered by a number of factors, and hence there has been a comparatively small number of reports using tactile stimulation compared to the abundance of eSEP studies over the last three decades. Previous groups have noted disadvantages, including a low signal-to-noise ratio due to a smaller scalp-recorded signal, poor synchronicity in the activation of fibres compared to an electrical stimulus (which may also contribute to a smaller response), uncertainty as to the temporal delay

between activation of the mechanical stimulus and of the receptor, and noise produced by the stimulator (Kakigi & Shibasaki, 1984; Cohen et al. 1985).

Vibration has been reported to be a relatively selective stimulus for the primary (type Ia) endings of muscle spindles (Hagbarth, 1973; Burke et al. 1976; Roll & Vedel, 1982; Roll et al. 1989), within which are receptors that reliably encode information about the dynamic characteristics of movement (Matthews & Stein, 1969). The sensitivity of muscle spindle Ia afferent endings to (tendon) vibration was first demonstrated in anaesthetised, decerebrate cats, in which the vibratory stimulus was applied to the tendon and muscle (Matthews, 1966; Brown et al. 1967). Since then, there has been further evidence to show that vibration at 60Hz excites type Ia muscle spindle primary nerve endings (Hagbarth, 1973; Burke et al. 1976; Roll & Vedel, 1982; Roll et al. 1989), but is less effective in activating cutaneous inputs (Talbot et al. 1968; Abbruzzese et al. 1980; Desmedt et al. 1983; Cohen & Starr, 1985).

Other studies have shown that vibration stimuli activate not only muscle afferent receptors, but also cutaneous and subcutaneous receptors and joint receptors in animals and man (for review see Abbruzzese et al. 1980; Ibanez et al. 1989). Previous literature has demonstrated that vibrational (at 50 to 60Hz stimulation frequency) and electrical stimulations used to trigger SEPs activate the same population of fibers, or at least overlapping populations (for example Pratt et al. 1979b; Abbruzzese et al. 1980; Jones, 1981; Ibanez et al. 1989). Several studies have suggested that muscle and cutaneous afferents project to different cortical areas (for review see Kaas, 1983; refer to Section 1.4.1 of Chapter 1). Area 3a of the primary sensorimotor cortex has been shown to receive short-latency input from primary muscle spindle afferents in man, primates and cats (for review see McCloskey, 1978; Kaas, 1983). This area is found in the depth of the central sulcus and is thought to be the transitional region between the sensory and motor cortex. In comparison, areas 1, 2, and 3b of the primary sensory cortex receive cutaneous and subcutaneous inputs (refer to Section 1.4.1 of Chapter 1). Functional imaging methods such as PET, MEG and fMRI have demonstrated activation of the primary and secondary sensory areas as well as other sensorimotor areas and subcortical structures following vibration applied to different parts of the skin surface (for example Fox et al. 1987; Seitz & Roland, 1992; Meyer et al. 1991; Coghill et al. 1994; Golaszewski et al. 1998). Similarly, electrical stimulation of the median nerve has been reliably shown to activate the primary somatosensory cortex (Grimm et al. 1998).

4.1.3.1 Early latency vSEPs

As with eSEPs, in this thesis particular attention is placed on the early (or first identifiable) scalp-recorded vSEP components in the normal and diseased brain. In this section, an outline is provided of the previous literature on the early latency vSEP components (between 20 and 50ms) in normal subjects. A brief summary of the literature on middle latency vSEP components is given in the Discussion (Section 4.4.1).

The early latency components of the vSEP are temporally delayed in comparison to electrical stimulation counterparts (as discussed in Section 4.1.2.1). The two predominant early latency components to mechanical stimuli (either vibrational or mechanical 'taps' to the skin surface) have been identified in the literature as the N30 and P40. Both of these components, however, have been reported with inconsistent latencies in the literature. The N30 component varies in latency between 24 and 35.5ms and the P40 varies between 34 and 47ms (Pratt et al. 1979b; Pratt & Starr, 1981; Kakigi & Shibasaki, 1984; Onofrj et al. 1990). Other components between these peaks have also been reported, for example the P30 or N37 (Nakanishi et al. 1973; Pratt et al. 1979b; Kakigi & Shibasaki, 1984). The location of the source of both of these components appears to lie in the contralateral parietal cortex (for example Kakigi & Shibasaki, 1984). The presence or absence of early latency components in the vSEP has been shown to depend on the intensity of the stimulation and the sampling rate. For example the lower stimulation intensity and sampling rate failed to show any components shorter than 50ms in a study by Hamalainen et al. (1990), compared to Mitchie et al. (1987).

4.1.4 Aims of this study

There are clear advantages to using vibrational stimulation in patients, particularly children, for the investigation of cortical sensorimotor function. There are, however, limited clinical data concerning vSEPs (Hrbek et al. 1968). In the present study, a technique to record vSEPs to the index and middle fingertip (supplied by the median nerve) is reported and compared with corresponding eSEPs to the median nerve at the wrist in a group of adult volunteers. The characterisation of the vSEP in adult controls will provide data for subsequent comparison with recordings from less co-operative subjects, including children (see Chapters 6, 7, and 8).

4.2 Methods

Recordings were carried out in ten adult subjects (4 males and 6 females, 6 right-handed), aged between 22-30 years and without self-reported evidence of neurological disease or symptoms suggestive of abnormalities of somatosensory function. Electrical and vibration stimuli were applied to the right hand. Subjects sat in a comfortable chair and were asked to watch a video placed 2 meters away to minimise eye movement.

4.2.1 Stimuli

The SEPs to electrical and vibrational stimulation were recorded from each subject in separate trials in a single session.

Electrical stimuli were delivered to the right median nerve via surface electrodes ('Neuroline') which were placed over the nerve at the wrist with the anode located over the posterior crease and the cathode approximately 3cm proximal to the anode. Square wave electrical pulses of 0.2ms duration were delivered at 2Hz using an isolated constant current stimulator (Digitimer Ltd, Model DS2), triggered by a computer. The sensory and motor thresholds for the electrical stimulus were determined for each subject. The sensory threshold (S) was the lowest intensity of electrical stimulation that was perceived in the thumb by the subject, and the motor threshold (M) the lowest intensity at which a visible twitch was seen in the thumb. The intensities used for stimulation were based on these M and S values. A stimulation level of M+S was chosen as it is known to be a point at which the cerebral potentials are consistently at or close to saturation, whilst still being well tolerated by the subject (Lesser et al. 1979).

Vibration stimuli were delivered to the distal phalanx of the index and middle fingertips. Fingertip stimulation was chosen since it was not possible to stimulate the median nerve in isolation at the wrist using a 'T-bar', and also because vibration of the 'T-bar' at the fingertips was more comfortable. Stimuli were delivered via a 'T-bar' attached to an oscillating coil. The coil was driven by a computer generated 60 Hz sine wave. The sine wave had a short rise time of 0.3 ms to ensure a rapid stimulus onset in an attempt to synchronously activate the fibres and minimise jitter of the evoked cortical responses. The use of a computer to generate the input to the oscillating coil ensures an identical movement of the 'T-bar' with each stimulus. Subjects were asked to gently rest the tips of their index and middle finger on to the 'T-bar', with their wrist supported. The

displacement of the 'T-bar' was set to 2mm, minimising the depression of the skin. No joint movement was observed during stimulation. Stimuli lasting 150 ms were applied at 1 per second, akin to a 'vibratory tap'. Any sound produced by the vibratory stimulator was masked by the noise from the video being watched by the subject.

4.2.2 SEP Recordings

A total of 62 scalp electrodes were applied based on a modified version of the International 10-10 system (Nz, F9, F7, F3, Fz, F4, F8, F10, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FC8, T9, T7, C5, C3, C1, Cz, C2, C4, C6, T8, T10, CCP3, CCP4, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, CPP5, CPP3, CPP1, CPP2, CPP4, CPP6, P9, P7, P5, P3, P1, Pz, P2, P4, P6, P8, P10, PO3, POz, PO2, O1, O2, Oz). The reference was placed between Cz and FPz and the 'ground' electrode placed between Fz and FPz. The electrodes were concentrated particularly over the sensorimotor cortices of both hemispheres (Figure 4.1). Continuous data were collected using a SYNAMP system and Neuroscan version 4 software, with a bandwidth of 0.05-200Hz, sampling rate at 5kHz, and amplified at x12500. Epochs from electrical and vibration stimuli were collected between -50 to 200 ms duration and had an average baseline calculated between -50 to -10 ms pre-stimulus. EOG artefact rejection was set at ±50uV at Nz, and at least 80% of the total number of epochs were calculated and averaged. Recordings were subsequently re-montaged with an average reference comprising F9, F3, Fz, F4, F10. Vibrational and electrical-recorded SEPs were digitally filtered off-line at 0.3-55Hz and 0.3-100Hz respectively; the vSEPs used a low pass filter of 55Hz to ensure no contamination of the SEP from the stimulus artefact. In each subject, at least two runs of each paradigm were collected and compared to ensure reproducibility. These two runs were then grouped to produce a grand average waveform.

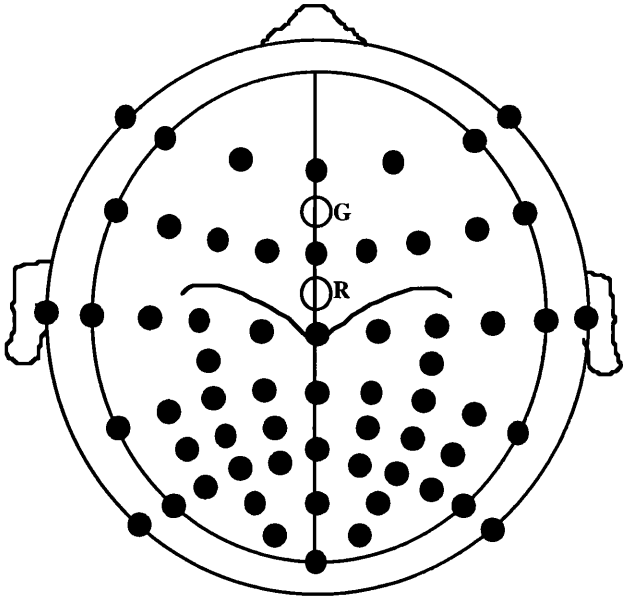


Figure 4.1: Montage used for vSEPs and eSEPs. R=reference electrode and G=ground electrode.

Many studies have reported that a large number of sweeps (up to 3000) need to be averaged in order to obtain a reproducible SEP, requiring the subjects to remain still and relaxed over relatively long periods of time (Kakigi & Shibasaki, 1984). For studies with young adults and children of differing mental abilities and poor concentration spans, the investigation had to be as short as possible, and remain effective at recording reproducible SEPs. Preliminary experiments leading to this study demonstrated that a large, clear and reproducible SEP to vibrational stimulation could be averaged from 400 stimuli. In this study, the total length of time to record one run of vSEPs (400 stimuli) was approximately six and a half minutes. In contrast, 200 sweeps were recorded for eSEPs, taking approximately one and a half minutes to acquire.

The most stable and recognisable components within the time interval of 15-200ms were identified in the waveforms. The peak latencies for each of the SEP components between 15-200ms were measured by visual placement of a cursor on a computer screen. Amplitudes were measured between alternating peak-to-peak components (Nuwer et al. 1994). All measurements were taken from electrode CP3 over the primary somatosensory cortex contralateral to the side of stimulus. Paired t-tests were performed between the latencies and amplitudes of identified vibrational and electrical components. Topographic 2-D surface voltage maps were constructed using Neuroscan version 4 and displayed as colour images.

4.3 Results

The majority of components evoked by electrical stimulation had vibrational evoked counterparts, with the exception of the electrical N35 component. The eSEPs and vSEPs recorded on electrical median nerve and vibration finger-tip stimuli in two of the subjects are shown in Figure 4.2 and Figure 4.3.

The components present in the eSEP on median nerve stimulation at the wrist were consistent with the many reports in the literature over the last few decades (refer to Sections 4.1.2.1 and 4.4). Based on the nomenclature reported by other groups, for the purpose of this study, the eSEP components are named as follows, as determined by their approximate latency and polarity; eN20, eP30, eN35, eP45, eN60, eP90, and eN130 (Table 4.1). The eN20, eP30, eP45, eP90, and eN130 components were seen in all of the volunteers; however, the eN35 and eN60 occurred in 70% of the volunteers.

The waveform on vibrational stimulation consisted of an initial negativity, followed by a further five components, alternating in polarity. A negative component between 45-55 ms was not clearly identifiable in most of the volunteers, and so this component was not included in the analysis of the data (labelled c in the eSEP of Figure 4.2). The potentials that were identified were designated, on the basis of their latency and polarity, as vN30, vP40, vP60, vN70, vP100, and vN140 (Table 4.3). These components correspond with the components listed in order of latency from eSEPs in Table 4.1. The vN30, vP60 and vN70 was consistently seen in 100% of the volunteers. The vP40 was seen in 60% of the volunteers and the vP100 and vN140 was seen in 80% of the volunteers.

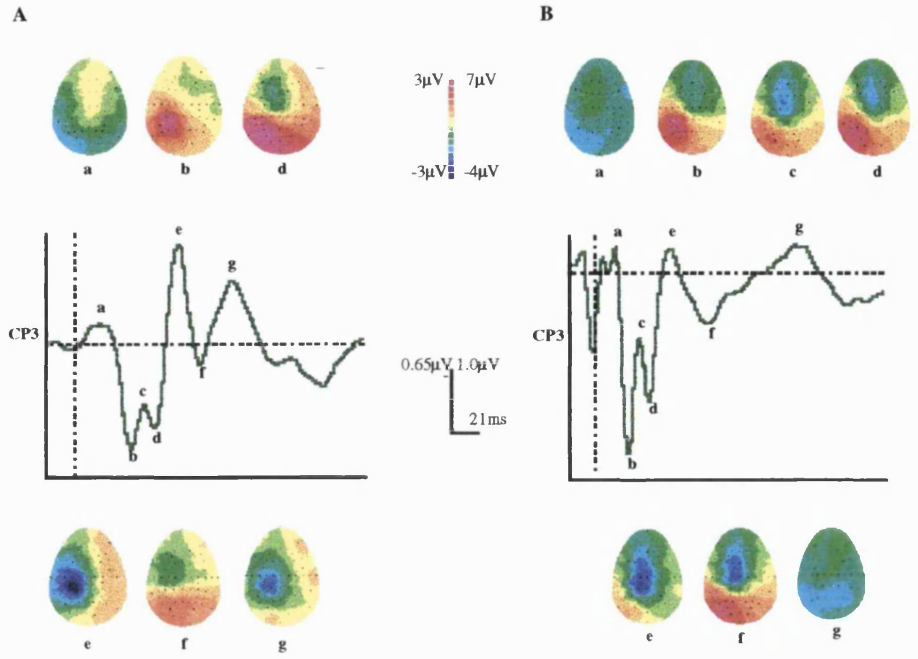


Figure 4.2: Comparative SEPs recorded in electrode position CP3 in response to vibrational (A) and electrical (B) stimulation for subject 1. Voltage maps are depicted that showed foci of peak voltage for individual components. Note the differences in amplitude of the waveforms and voltage window for the map.

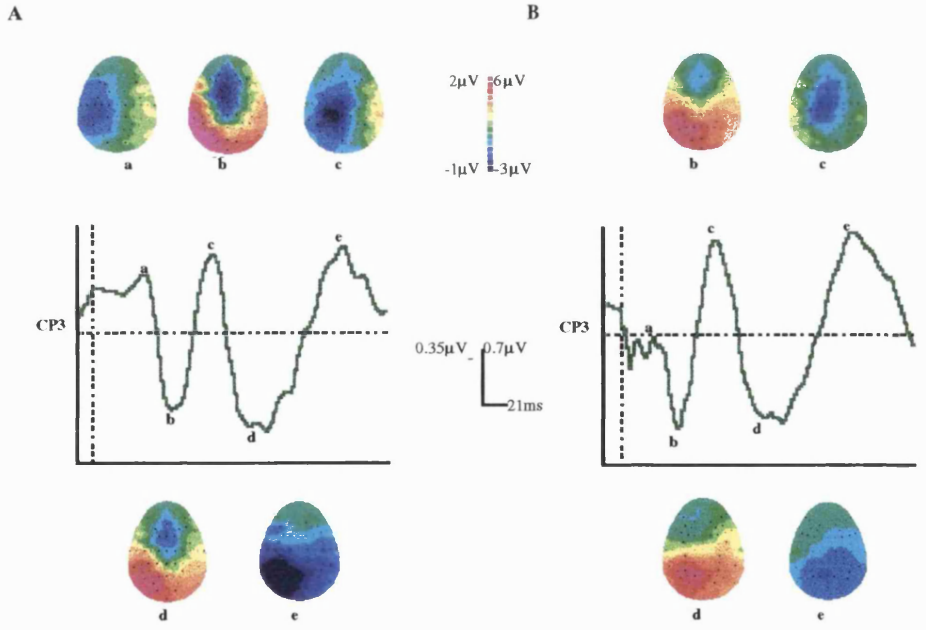


Figure 4.3: Comparative SEPs recorded in electrode position CP3 in response to vibrational (A) and electrical (B) stimulation for subject 2. Voltage maps are depicted that showed foci of peak voltage for individual components. Note the differences in amplitude of the waveforms and voltage window for the maps.

The field distributions of the comparative components on the scalp following vibrational and electrical stimulation are shown as 2-D colour voltage maps (Figure 4.2 and Figure 4.3). The voltage distribution of the maps was seen to be almost identical, across the

two stimulation modalities employed. The peak response for all components was located in an area including electrode CP3 or P3, which overlies the contralateral primary sensorimotor area.

	Peak Latency Analysis						
	1	2	3	4	5	6	7
Average Latency (± Standard Deviation)	18.79 ±1.82	27.24 ±3.2	34.46 ±4.59	44.92 ±5.5	59.65 ±5.13	86.41 ±12.92	133.00 ±11.15
Polarity	N	P	N	P	N	P	N
% Occurrence	100	100	70	100	70	100	100
Approximate Maximal Location (From Voltage Maps)	c/l SM area P3	c/l SM area CP3	c/l SM area CP3	c/l SM area CP3	c/l SM area CP3	c/l SM area P3	c/l SM area CP3
Component name	eN20	eP30	eN35	eP45	eN60	eP90	eN130

Table 4.1: Components present in the SEP in electrode CP3 following electrical stimulation of the median nerve at the wrist in 10 volunteers. 'N' and 'P' represent negative and positive components respectively, c/l SM refers to the contralateral sensorimotor cortex at the specified electrode locations.

Components amplitude	eN20/eP30	eN20/eP45	eP45/eN60
Mean	3.8	5.39	4.75
Standard Deviation	2.49	2.65	1.75
% Occurrence	100	100	70

Table 4.2: Amplitude measurements between major peak components specified in Table 4.1 in 10 volunteers following right median nerve electrical stimulation.

	Peak Latency Analysis					
	1	2	3	4	5	6
Average Latency (± Standard Deviation)	29.4±5.0 ***	41.8±3.5 **	59.8±3.0 ***	76.0±5.8 ***	96.5±7.2 *	151.25±24.2
Polarity	N	P	P	N	P	N
% Occurrence	100	60	100	100	80	80
Approximate Maximal Location (From Voltage Maps)	c/l SM area P3	c/l SM area P3	c/l SM area P3	c/l SM area CP3	c/l SM area P3	c/l SM area CP3
Component name	vN30	vP40	vP60	vN70	vP100	vN140

Table 4.3: Components present in the SEP in electrode CP3 to right index and middle finger vibrational stimulation in 10 volunteers. 'N' and 'P' represent negative and positive components respectively, c/l SM refers to the contralateral sensorimotor cortex at the specified electrode locations. The vSEP components that were significantly longer in latency than the eSEP components are indicated (*=$p<0.05$,**=$p<0.005$,***=$p<0.0005$).

Components amplitude	vN30/vP40	vN30/vP60	vP60/vN70
Mean	1.73*	3.03*	2.6
Standard Deviation	1.09	1.48	1.91
% Occurrence	60	100	100

Table 4.4: Amplitude measurements between major peak components specified in Table 4.3 in 10 volunteers following right vibrational stimulation. * indicates the vSEP components that were significantly smaller in amplitude compared to the corresponding eSEP components (*=$p<0.05$).

Differences were observed between the peak latencies and peak to peak amplitudes of the identified eSEP and vSEP components (compare results in Table 4.1 and Table 4.2 recorded following electrical stimulation to those in Table 4.3 and Table 4.4 following vibrational stimulation). There was a statistically significant increase in the latency of the early components of the vSEP compared to the eSEP ($p<0.05$ for all comparisons between vibration and electrical components), with the exception of the eN130 and vN140 component, in which the difference did not reach statistical significance ($p=0.08$). In addition, for the vN30/vP40 and eN20/eP30 ($p<0.05$) and the vN30/vP60 and eN20/eP45 SEP components ($p<0.05$), the amplitudes were significantly smaller with the vibration than with the electrical stimulus. The comparative vSEP components were reduced in size by up to half when the fingertip was mechanically stimulated (in agreement with Onofrj et al. 1990). However, there was no statistically significant difference between the amplitude of the vP60/vN70 and the eP45/eN60 SEP components ($p=0.1$).

Paired t-tests were also carried out to compare the peak to peak latency of sequential component intervals to electrical and vibration stimuli. There was no significant difference in latency between the eN20 to eP45 and the vN30 to vP60 ($p=0.14$; electrical mean±SD=26.1±6.3, vibrational mean±SD=30.4±5.4), or between the eP30 to eN60 and the vP40 to vN70 (electrical mean±SD=33.7±5.0, vibrational mean±SD=33.0±2.4, $p=0.77$).

Following the session, all of the volunteers reported feeling less discomfort during vibration as compared to electrical stimuli, despite the increased duration of recording in the former.

4.4 Discussion

This study has demonstrated that reproducible scalp SEPs can be recorded to a vibration stimulus applied to the finger tips that are comparable to the SEPs to median nerve electrical stimulation. These findings are similar to those reported previously (Kakigi & Shibasaki, 1984; Hamalainen et al. 1990). In addition, the voltage maps were visually almost identical in distribution, between the two stimulation modalities employed. vSEP components were longer in latency and smaller in amplitude than their eSEP counterparts.

Several previous reports comparing vSEPs and eSEPs have shown differences in the number of components within the same time window analysed (Pratt et al. 1979b; Pratt & Starr, 1981). The authors of these studies have suggested that this difference may be explained by the mechanical stimulus they employed failing to activate a sufficient number of neurones that are required to produce a recordable response from the scalp surface. It has also been suggested that there are differences in the afferent fibre input resulting from the two kinds of stimulation (see Section 4.1.1). Electrical stimulation activates a larger variety of fibre types and neural pathways through stimulation of the nerve trunk compared to mechanical stimulation which activates a smaller number but overlapping population of fibres (for example Pratt et al. 1979b; Abbruzzese et al. 1980). It may also reflect differences in the degree of synchrony of the activated fibres resulting from the stimuli used. However in this study, as only one vSEP component was not reproducibly observed that was seen in the eSEP waveform, it appears that both stimuli activate similar fibres and an adequate number to produce SEP responses. Our finding supports those of some previous studies where responses to tactile stimulation were reported to be similar in morphology to those evoked by peripheral nerve shock (Larsson & Prevec, 1970; Pratt et al. 1979b; Pratt & Starr, 1981; Kakigi & Shibasaki, 1984; Hashimoto et al. 1990; Onofrj et al. 1990).

In general, vSEP components were of significantly lower amplitude and longer in latency than their eSEP counterparts. A significantly smaller amplitude of the scalp-recorded vSEP compared to eSEP is in agreement with previous studies (Nakanishi et al. 1973; Pratt & Starr, 1981; Kakigi & Shibasaki, 1984; Cohen et al. 1985). Onofrj et al. (1990) reported a reduction of the size of the vSEP of up to half of that with eSEPs. This smaller amplitude of vSEP components may reflect a smaller number of fibres activated or the poor synchronicity of the stimulated fibres with vibration (see below) compared to those activated by electrical stimulation. The reduction in amplitude of the

vSEP compared to eSEP response may also be a reflection of the difference in the site of stimulation (the wrist for electrical stimulation and fingertips for vibrational stimulation) (Onofrj et al. 1990). Vibration applied to two fingertips only stimulates a proportion of the median nerve supply to the hand, whereas electrical stimulation applied at the wrist stimulates the whole nerve trunk.

As in this study, other reports have shown differences between the peak latency of comparable components in mechanically and electrically evoked scalp responses. A number of studies have reported a 1 to 6 ms increase in the latency of scalp-recorded mechanical SEP components compared to those in eSEPs (for example Pratt et al. 1979b; Pratt & Starr, 1981; Kakigi & Shibasaki, 1984; Onofrj et al. 1990). Indeed, slower nerve conduction velocities in response to mechanical as compared to electrical stimuli have been reported (Nakanishi et al. 1973; Buchthal, 1980; Caruso et al. 1994, 1993). However in this study, there was no significant difference between peak to peak latency measurements for the early latency components. Several studies have suggested that the latency difference may be due to a time lapse from the onset of vibrational stimulation on the skin to the actual excitation of the median nerve, rather than a difference in the conduction velocities of the fibre types activated by electrical versus vibration-responding receptors (Nakanishi et al. 1973; York, 1985; Hashimoto et al. 1990; see Caruso et al. 1994 for discussion). In addition, electrical stimuli have been shown to give rise to single synchronous nerve action potentials (via many nerve fibre types), while vibration results in continuous firing in the fast-conducting mechanoreceptor fibres (Pratt et al. 1979b). The mechanoreceptors in question are most likely the fact-adapting Pacinian and Meissner corpuscles (Mountcastle et al. 1969; Pratt et al. 1980; Mogilner et al. 1994) or primary muscle spindle endings (Burke et al. 1976; Cohen et al. 1985). Alternatively, this difference in latency between components following electrical versus mechanical stimuli may be attributed to the high degree of synchronicity within stimulation of thalamocortical fibres on electrical stimulation (electrical stimuli will give single synchronous nerve action potentials), whereas during mechanical vibration, bursts of individual stimuli are delivered to the thalamocortical fibres which may be dispersed in time in relation to each other and not so reproducible (due to continuous firing in the fast-conducting mechanoreceptor fibres) (Larsson & Prevec, 1970; Pratt et al. 1979b). In the present study, however, the short rise time of the sine wave used to drive the 'T-bar' for vibrational stimulation increases the synchronicity of activation of the median nerve fibres and reduces jitter in the vSEP. Finally the difference in the peak latencies between the vSEP compared to the eSEP response may also be a reflection of the difference in the site of stimulation (the wrist for electrical and fingertips for vibrational). The estimated time for the increased

distance, i.e. from finger tips to wrist, is only approximately 4 ms (McQuillen & Gorin, 1969); therefore such a mechanism could only partially account for the 10 ms latency difference seen in this study.

4.4.1 Summary of individual components

In this study, the distribution of the scalp responses in the voltage maps was very similar between comparative components in the vSEP and eSEP waveforms. The peak response was located in the contralateral primary sensorimotor area for all of the components mapped. There was no evidence of isolated ipsilateral SEPs to vibration or electrical stimuli.

The first scalp-recorded component in response to vibrational stimulation was the vN30. This component seems to correspond to the eN20 in this study. Both of these components were located in the contralateral hemisphere to the stimulus (within the parietal cortex) in agreement with previous studies (for a review of the literature on the eN20 and vN30 component, refer to Sections 4.1.2.1 and 4.1.3.1, respectively). Usually this component in both eSEPs and vSEPs shows an anterior-posterior contralateral inversion, as seen in the voltage maps of subject 1 and 2 in Figure 4.2 and Figure 4.3 (for example, Desmedt et al. 1987; Allison et al. 1989a; Onofrj et al. 1990).

Electrical stimulation studies have also reported a component between 22-25ms called the eP22, eP24 or eP25, which is smaller in amplitude than the eN20 component and less reproducibly observed (Desmedt & Cheron, 1980, 1981; Allison et al. 1991a). The eP22/24/25 component, or an equivalent vSEP component, was not reproducibly observed in the wave forms in this study.

The vP40 component appears to correspond to the eP30 SEP component. As with the eN20 and vN30 components, this first positive component to electrical and vibrational stimulation is located in the contralateral parietal cortex. This location is consistent with many previous observations for both stimulus types (for example Nakanishi et al. 1973; Pratt & Starr, 1981; Kakigi & Shibasaki, 1984; Wood et al. 1988; refer to Sections 4.1.2.1 and 4.1.3.1).

The second positive peak in the vSEP in this study was identified as the vP60 component, and corresponded to the eP45 in the eSEP. The vP60 component has been identified in previously reported vSEP studies and is likely to be the high frequency P50

reported by Hamalainen et al. (1990), the high frequency P1 component introduced by (Feinsod et al. 1973), the P55 component (Mitchie et al. 1987), the P49 potential (Kakigi & Shibasaki, 1984) and finally the 58.6 and 52.3 ms steady state potentials in a study by Snyder (1992). The eP45 component has also been described in previous studies (for example Goff et al. 1977; Ikuta et al. 1980; Nagamine et al. 1992). The topographical maps in Figure 4.2 and Figure 4.3 show that the vP60 and the eP45 are located in the contralateral parietal cortex, with an anterior-posterior polarity reversal.

The vN70 component was focally observed in centrally located electrodes (see Figure 4.2 and Figure 4.3). This component seems to correspond with the eN60 component in the eSEP waveform. The vN70 and eN60 components have been reported in previous studies (Kakigi & Shibasaki, 1984; Hamalainen et al. 1990; Yamada et al. 1984; Huttunen, 1995); however their origin is unclear and still a matter of debate (for review see Treede & Kunde, 1995). The vN70 wave may originate in the contralateral S1 somatosensory area (Hamalainen et al. 1990); however, the bilateral nature of the component does not rule out a participation from other association areas such as the S11 area.

The vP100 and equivalent eP90 components were seen most focally over the contralateral sensory cortex in the topographical maps constructed. The report of (Hamalainen et al. 1990) also noted a larger contralateral voltage peak of the vP100 (also revealed by Desmedt & Robertson, 1977), but showed the distribution to be more bilateral than in this study. They proposed that the vP100 in their study reflected contra- and ipsilateral activation of the S11 cortices, an idea which does not appear to be supported by the distribution of the vP100 component recorded in response to vibration in the present study (also supported by Hamalainen et al. 1988; and MEG studies by Hari et al. 1983, 1984).

Finally, the vN140 and eN130 peaks reside primarily in the contralateral sensorimotor cortex, in the more anterior and central located electrodes on the scalp. This is in agreement with previous vibration studies reporting the component to be asymmetrically represented in the brain (larger contralaterally) and most likely generated by several mechanisms which are still to be determined (Desmedt & Robertson, 1977; Hamalainen et al. 1990). The vN140 component, along with later components, has been shown to be involved in conscious somatosensory target detection or discrimination during an odd-ball paradigm using vibration stimuli of differing frequencies (Kekoni et al. 1996). The eN130 (or equivalent) has also been identified in previous studies (for example

Treede & Kunde, 1995) and has a topography consistent with a generator in the vicinity of the S11 area.

4.5 Conclusions

The present study has demonstrated that SEPs can be reliably recorded in response to vibrational stimulation in adult normal controls. Vibration is a painless, natural stimulus compared to electrical stimulation and therefore would be a more appropriate method for activating the somatosensory cortex in less tolerant patients, such as children. A combination of these methods has previously been applied to numerous clinical problems of somatic sensation that accompany neurological disorders, to assist in the localisation and definition of the mechanisms of the sensory impairment (for example Nakanishi et al. 1974; Lorenz et al. 1996). This study confirms that vibrational stimulation may be an alternative or additional method to electrical stimulation for the activation of the sensorimotor cortex in SEP recordings in normal controls and in patients with brain disease.

Chapter 5: Behavioural measures of sensorimotor function - methodology

5.1 Introduction

Much information on the cortical localisation of sensorimotor function has been gained from clinical descriptions of patients with circumscribed brain lesions. Many studies have reported on somatosensory and motor function following brain injury and neurosurgery (for example Muller et al. 1991), and neuropsychological tests allow a systematic and quantitative way of assessing any residual function. This chapter describes the behavioural tests used in this study to assess somatosensory and motor functioning. This allows comparisons to be made between the results of fMRI and SEP findings and the actual functional sensory and motor capabilities of patients with brain damage.

It is a well-known phenomenon that the distal parts of the limb are controlled primarily by the contralateral sensorimotor cortex; however, more proximal parts of the limb and body trunk are controlled via bilateral cortical projections (Lawrence & Kuypers, 1968; Ghez, 1991). A previous investigation into residual sensorimotor function in patients with hemispherectomy surgery revealed a distal to proximal gradient, distal functioning always being the most impaired and so lending itself to be the most likely to show cortical reorganisation (Dijkerman, 1996). Therefore, when investigating reorganisation of sensorimotor function, particularly in terms of ipsilateral as well as abnormal contralateral projections, it is clear that the distal part of the limb should be considered. This chapter outlines a variety of sensory and motor functions that have been tested, mainly concentrating on hand function. As the majority of patients investigated for this thesis have been children, the neuropsychological tests have been carefully chosen in order to make the tests easy to understand and to keep the assessment time relatively short (approximately half an hour in total).

Attention has been focused on the residual sensory and motor functioning contralateral to the lesioned hemisphere (contralesional side), but the function of the ipsilesional side has also been assessed to act as a 'control' for the defective side, as with the fMRI and SEP methodology. Although this intra-patient approach dominates this study, a number of studies investigating sensorimotor function in patients with brain damage using the

techniques described below have compared the patient data to those collected in normal controls (for example Corkin et al. 1970; Leonard et al. 1988).

The following somatosensory functions were tested: joint position sense and double simultaneous stimulation of hand. The motor tasks were finger tapping and peg sorting (to examine speed and dexterity of finger movements and co-ordination), and force production.

5.2 Methods

5.2.1 Sensory Tests

5.2.1.1 Joint position sense

Procedure: The subject's distal phalanx on each finger was moved six times up and six times down by the investigator in a randomised order. The investigator holds the distal phalanx joint in one hand and moves only the tip of the finger with the other hand. The patient judges the direction of movement and replies with 'up' (finger extension) or 'down' (finger flexion) whilst blindfolded. The test was first applied to the ipsilesional side and then repeated on the contralesional side starting with the thumb and proceeding across all four fingers to the little finger of each hand. The procedure is also described by Corkin et al. (1970), where it was used with a group of patients with unilateral cortical excisions and a group of normal adult controls. They showed that 99% of the adult controls scored over 57 out of 60 correct, and there were no systematic differences between the left and right hands. There have been no data reported using joint position sense to assess sensory function in normal child controls.

Scoring: For each of the fingers the number of correct answers out of 12 movements was recorded (a total of 60 moves in each hand).

5.2.1.2 Double simultaneous stimulation - hand

Procedure: The patient was instructed to place both hands flat on the table top, palm down, and fingers spaced apart. The investigator strokes a finger on the patient's hand (from top of the finger to the bottom in a single motion), either in isolation or simultaneously, with a finger on the other hand. The patient wore a blindfold and indicated, by either saying the number of the finger(s) (thumb numbered 1, little finger numbered 5), finger movement or pointing to the finger(s) with the opposite hand, where he/she had been touched. Each combination of finger touching was tested in a set

order which prevented biasing. The purpose is to look for possible extinction or erroneous localisation of stimuli to one hand, either in the presence or absence of a competing input to the other hand (Bender, 1945). One study in children, using a similar method to the one described here, showed a general reduction in the number of errors from 6 year to 14 years (from a mean value of two errors made at 6 year to less that 0.5 errors made at 14 years), and there were no differences in the performance of either hand at any age (Finlayson & Reitan, 1976).

Scoring: The data were reported as the number correct when one or two finger(s) were touched for the left and right side separately.

5.2.2 Motor Tests

5.2.2.1 Tapping

The purpose of this test was to measure the motor speed of the index finger in order to assess residual motor function. The method has previously been described elsewhere and shown to be a useful method to assess handedness (Peters & Durling, 1979; Peters, 1981).

Procedure: Finger tapping was carried out using a manual tapper mounted on a wooden board connected to an electronic counter. The subject was asked to place the hands flat onto the board (palm down) and lift the index finger only so that it reached comfortably onto the switch. They were instructed to make 'taps' with their index finger (i.e. to depress the switch) as many times as possible in 20 seconds (timed on a stop watch by the investigator), keeping all the other fingers flat on the board throughout. The number of taps was automatically recorded by the counter. The test was performed twice with each hand, starting with the ipsilesional hand and alternating between the two sides. In addition, to assess the presence of mirror movements, the hand not tapping was rested on the table and observed for any movement which clearly mimicked tapping in the index finger of the opposite hand.

Scoring: For each hand, the mean number of taps was calculated from two trials.

5.2.2.2 Force Production

Grip strength is one of the most widely-used clinical measures of human hand strength and has been used with a variety of other measures to assess hand function (Boll, 1974; Reitan, 1974; Broadhead, 1975; Finlayson & Reitan, 1976; Dodrill, 1978; Agar et al. 1984; Newman et al. 1984). However, a large variety of methods have been adopted

and modified to measure grip strength in adults and children (for a summary of the literature see Dunn, 1992). These different procedures have made the data on grip strength inconsistent and incomparable. For the purpose of this study only one method of grip strength was selected, which could also be used in children. This was adapted from a method used by Leonard et al. (1988).

Procedure: A kiddie hand dynamometer (Smedley, model 78011, La Fayette Company, 1989) was used to measure grip strength in kg. The device consisted of a handle connected to a force transducer (two metal plates separated by a spring device recording the amount of pressure being placed on the device). Subjects were asked to stand with both feet together and to hold the dynamometer handle with one hand so that the forearm and upper arm were at right angles (the dynamometer was raised for taller patients as appropriate). The length of the dynamometer handle was adjusted to the size of the subject's hand. The patient squeezed the handle with his/her hand as hard as possible. Three trials were performed with each hand, starting with the ipsilesional side, and continuing in a set order to prevent bias.
Scoring: For each side, the mean and standard deviation of the force produced were calculated from 3 trials.

5.2.2.3 Peg sorting

This procedure was first designed and developed by Annett in the early 1970s (Annett, 1970a & b). It has been found to be a reliable and easily applied method to assess finger dexterity and co-ordination in normal adults and children (Annett, 1983; Annett & Kilshaw, 1983; Kilshaw & Annett, 1983).

Procedure: A peg board was used which consisted of two rows of ten holes. Ten short (2 cm) wooden pegs were placed in the top row of holes, and the patient was instructed to stand with his/her feet together and move the pegs one at a time into the corresponding hole in the bottom row as quickly as possible. The left hand started with the peg on the far left side, so that movements were made across to the right side as each peg was placed, and vice versa. The procedure was timed with a stop watch and five trials were performed with each hand, starting with the ipsilesional hand and alternating thereafter.
Scoring: The mean and standard deviation of times recorded for each hand were calculated over five trials. The results indicated that the longer the time taken to move the pegs, the more impaired the patient's hand.

5.2.2.4 Mirror movements

Procedure: Mirror movements are 'involuntary synchronous movements of one limb during intended movements of contralateral homologous body parts' (Nelles et al. 1998), and they predominantly affect the small hand muscles (Rasmussen, 1993). In this study, mirror movements were assessed using three tests. All of the tests were carried out with the patient's elbows placed on a table top with the hands in the air. The patient was asked to concentrate on and move his/her ipsilesional hand in each case and to keep his/her contralesional hand as still as possible. Firstly, they were asked to perform a simple finger to thumb opposition task, firmly touching each finger onto the tip of the thumb in turn. Secondly, a fist was made with both hands and the patient was asked to rotate his/her hand in a clockwise/anticlockwise motion. Finally, the hand was positioned flat, the fingers outstretched, and the patient was requested to move his/her fingers as if 'playing the piano', each finger performing discrete depressions (as detailed in Woods & Teuber, 1978). The presence of mirror movements in the contralesional hand that could be associated directly with identical movements made with the ipsilesional hand was noted. The presence of mirror movements were also noted as in the tapping test (see Section 5.2.2.1).

5.2.2.5 Handedness

Although right-handedness is the norm, a substantial minority of people are left-handed and a few are ambidextrous (Ellis et al. 1988). The factors that may be responsible for this individual variation in handedness have been a topic of debate. The importance attributed to genetic and environmental factors as a basis for handedness have varied (for review see Bishop, 1990). For example, one possibility is that familial sinistrality can be used as an index. However, several studies have shown that familial sinistrality is an inaccurate index of genetic tendencies to left-handedness [for example Annett (1985) showed that for a left-handed child, the probability of having at least one left-handed parent is around 0.24]. In contrast, a very different type of aetiological theory on hand preference was put forward by Bakan (1971) and Bakan et al. (1973), who maintained that left-handedness was a manifestation of underlying brain damage sustained around the time of birth. A further study noted that very preterm children were more vulnerable to brain damage and therefore a change in hand preference (O'Callaghan et al. 1987). Although Bakan's hypothesis that attributes all left-handedness to pathological factors is not widely accepted, it does seem plausible to suppose that brain damage may play a role in determining handedness in some individuals. Possible indicators of pathological or non-pathological left-handedness that have been used are the strength of hand preference

(Subirana, 1969), the observation of restricted growth in one limb (Satz et al. 1984), and clumsiness of the non-preferred side (Bishop, 1980).

Studies have shown that even when there is no severe hemiplegia, early damage to the left hemisphere can result in left-handedness (for example Vargha-Khadem et al. 1985; Orisini & Satz, 1986; Satz, 1988). These studies of pathological left-handedness without hemiplegia raise the question of whether the phenomenon of pathological left-handedness occurs only when there is clear evidence of brain damage, or whether less evident neurological abnormality might be responsible for increases in the frequency of left-handedness in certain clinical conditions where there is no obvious brain damage. One recent study has shown an increase in the incidence of left-handedness in patients with left hemisphere damage; however this was unrelated to the age at injury (Isaacs et al. 1996). The major difference between this study and previous studies demonstrating a relationship between the age at injury and a shift in handedness (for example Orisini & Satz, 1986), is that the latter studies included children with lesions located outside the sensorimotor system. In the study of Isaacs et al. (1996), all of the children had damage which included the sensorimotor system, leading to a shift in handedness in nearly all cases with left hemisphere damage, regardless of age at injury.

It is standard practice in the report of neurological cases to describe the patient as right- or left-handed. More subtle differences in handedness which may occur, for example, in patients with discrete sensorimotor lesions can only be assessed by more rigorous assessments. A number of techniques have been developed to ascertain hand laterality, and all are very similar to the one adopted and described in this study.

Procedure: A questionnaire was used to assess handedness, performed using a method adapted from Crovitz & Zenner (1962). The degree of hand preference was estimated by asking the subjects to indicate which hand they normally used to perform 18 common actions (for example brushing teeth, using a key), some of which were bimanual (for example slicing bread). The patient is asked to indicate on a 5-point scale (right always, right mostly, both equally, left mostly, left always) which hand would normally be used to perform each of the tasks.
Scoring: Scores of hand performance for the final questionnaire fall between 18 (completely right handed) and 90 (completely left handed). Ambidextrality lies between 31 and 55.

5.3 General comments

A note was made at the end of the assessment of the child's general motor and sensory abilities on a day to day basis (for example if they have ever damaged their hand and not felt it, or whether they used one hand as merely a 'support') as reported by the parents or the child. Due to the different cognitive abilities of the children, several patients were unable to complete all the tests. In very young or cognitively impaired children, either the assessment was kept to a minimum (i.e. tapping, force production, and Annett pegs), or simplified tasks such as simply covering the child's eyes and asking them to say when the back of their hand or fingers was touched were used.

Chapter 6: Adult and child control data.

6.1 Introduction

As reviewed in Sections 1.3.4.1 and 1.4.3.3 of Chapter 1, sensory and motor fibres have been reported to exist between the distal portion of the limb and the ipsilateral sensorimotor cortex in normal adults and children. Studies have suggested that reorganisation or unmasking of these connections may account for the extensive recovery of sensorimotor function that has been reported to occur after unilateral brain injury (Benecke et al. 1991). The existence of ipsilateral, as well as contralateral, sensorimotor responses in normal adults and children is critical to our understanding and interpretation of the reorganisation of sensory and motor systems in patients with brain disease.

6.1.1 Aims of this chapter

In this chapter, paradigms to assess the pattern of brain activation in normal healthy subjects are described. These paradigms firstly must be reliable in activating the primary sensorimotor cortex, and secondly must be suitable for use in patients with sensorimotor deficits of the hand. The results of applying such paradigms in fMRI, SEP and behavioural investigations of sensory and motor function are reported in groups of adult and child controls.

6.2 Methods

The paradigms adopted below were applied to both the left and right hand in each subject.

6.2.1 Behavioural Tests

For comparison with behavioural data collected from the patient groups described in Chapters 7 and 8, a full battery of the sensory and motor tests detailed in Chapter 5 was carried out in the child controls. Each subject's handedness was assessed using the questionnaire described in Section 5.2.2.5 of Chapter 5 (Crovitz & Zenner, 1962).

6.2.2 fMRI

Three experiments were performed in control subjects, namely active movement, passive movement and electrical stimulation. fMRI data were acquired and analysed using the box car paradigm described in Section 1.4 of Chapter 3. Activation maps were spatially smoothed to three times the original voxel size. All figures showing images of fMRI activation are displayed as axial slices taken through the sensorimotor cortex in anatomical convention (left on the image is left of the brain). Images are displayed at an uncorrected p value threshold of $p<0.01$, extent threshold of $p<0.05$.

6.2.2.1 Active versus passive hand movement

Two hand motor tasks were performed by a group of adult and child volunteers, one active and one passive. The tasks were carried out separately with both hands. Both tasks involved flexion/extension of the metacarpophalangeal joint, and were carried out at a rate of approximately 2 Hz. For the active movement task, the subject was instructed to carry out a hand grasping motion, moving the fingers in unison in and out of the palm, keeping the fingers as straight as possible throughout. Passive movement was performed with the subject's arm, hand and fingers fixed to a support with Velcro straps and the fingers flexed via a rod attached to the distal end of the support (see Figure 6.1). The hand was fixed to the support throughout the investigation, so no additional sensory stimulation occurred during the performance of the task compared to the rest condition. The volunteers were able to relax the hand fully and allow the examiner to move it, reducing the urge to move the hand themselves. In order for direct visual comparisons to be made between active and passive movement, the two types of dataset were acquired in the same scanning session. A paired t-test was performed between the percentage signal change values (acquired as described in Section 3.2.2 of Chapter 3) measured in a region of activation in the contralateral sensorimotor cortex following active movement and passive movement.

a) b)

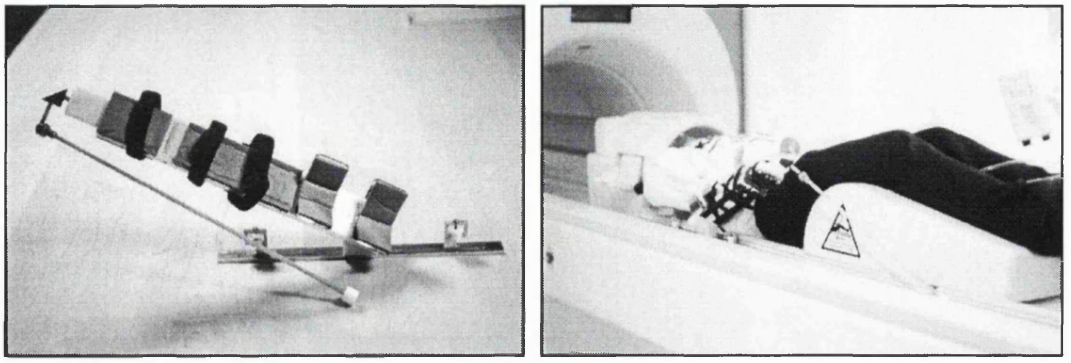


Figure 6.1: Arm and hand restraint using for passive movement stimuli during fMRI. a) shows the support with Velcro straps attached and b) the support in place on a child lying outside of the magnet.

6.2.2.2 Left versus right hand movement in controls with left or right hand dominance

fMRI was carried out in a group of normal adult volunteers to investigate activation in response to an active motor task performed with the dominant and non-dominant hand. In addition, passive movement of the dominant and non-dominant hand was carried out in a group of child controls. As data from an individual were acquired within the same session, datasets could be realigned and analysed together and comparisons made between each hand for both tasks. A description of the tasks is given in Section 6.2.2.1.

6.2.2.3 fMRI with electrical stimulation

In a group of adult controls, electrical stimuli were applied to the median nerve via surface electrodes that were placed on the wrist, in an identical fashion to that described in Section 4.2.1 of Chapter 4. Stimuli were delivered at a rate of 4 Hz; this frequency has been shown to maximally activate the primary sensory cortex (Ibanez et al. 1995), and also to show activation of the sensorimotor cortex on fMRI (Spiegel et al. 1999, see Section 2.3.1.3 of Chapter 2). A pulse duration of 0.2 ms at a stimulation intensity above motor threshold (a visible twitch obtained in the thumb) was used. The electrical constant current stimulator was driven within the magnet room via an external signal generator connected by an optical fibre from outside the shielded examination room. Stimuli were applied to the dominant or non-dominant hand in each volunteer, with the order chosen randomly. Active thumb or hand movement was also carried out in the same session consisting of opposition of the thumb across the palm or movement of the fingers into the palm. The rate of opposition was as fast as the subject could maintain throughout the 'on' task period, approximately 3 Hz in most cases. In three volunteers,

fMRI following electrical stimulation was carried out in 2 separate sessions to determine the reproducibility of the observed activation.

6.2.3 SEP recordings

SEPs recorded following electrical and vibrational stimulation were obtained for both left and right hands. The methods for both paradigms were identical to those described in Section 4.2 of Chapter 4. Electrical stimuli were applied to the wrist at a level set at motor plus sensory threshold (Lesser et al. 1979), which evoked a muscle twitch in the thumb. Vibration stimuli were delivered to the index and middle fingertips. The ground electrode was placed on the head slightly anterior to electrode position Cz, and averages referenced to three ipsilateral frontal electrodes to the side of the stimulus (F3/4, F7/8 and F9/10). Figure 6.2 shows the symmetrical 64 channel montage used in the study. In two of the less co-operative children a smaller number of electrodes was applied; however, the electrodes covered a similar distribution to that shown in Figure 6.2.

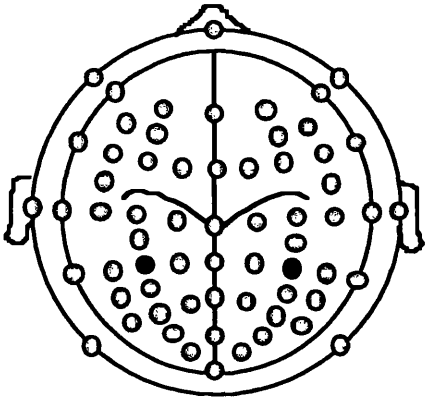


Figure 6.2: Montage used for electrical and vibrational SEP recordings in control subjects. Electrodes shaded red indicate the waveforms displayed in subsequent figures, and are the ones from which latency and amplitude measurements of the first cortical component were taken in all subjects.

Latency, polarity, and amplitude measurements of the early cortical components (N20/P30 and N30/P40 for electrical and vibrational stimulation respectively, see Section 4.4.1 of Chapter 4) were obtained from symmetrical electrode positions ipsilateral and contralateral to the stimulus (cp3 and cp4, shown in Figure 6.2). Topographic 2-dimensional surface voltage maps were subsequently constructed, with individual peaks mapped. All components demonstrating clear and focal voltage peaks in the maps were collected. Paired t-tests were performed between recordings from the

contralateral and ipsilateral hemisphere and between responses to stimulation of the dominant and non-dominant hands.

6.3 Results

The results for the adult and child controls are presented separately below.

6.3.1 Adult Controls

6.3.1.1 fMRI

6.3.1.1.1 Active versus passive movement

Data from ten adult controls (6 females and 4 males, age range 22-29 years, mean age 25.5 years) were obtained. Four volunteers were left handed (range of scores on the handedness questionnaire was 62-89; mean 79) and six were right handed (range of scores on the handedness questionnaire was 19-28; mean 23.8). The individual scores lay within the boundary values for left (score 56-90) and right (18-30) handedness, as proposed by Crovitz & Zenner (1962). All controls were volunteers without neurological disease or symptoms suggestive of abnormalities of sensorimotor functioning.

All 10 volunteers demonstrated contralateral primary sensorimotor cortex activation on active and passive movement of the left and right hands. In all volunteers, sensorimotor cortex activation was similar in location for the active and passive hand tasks. Three examples of contralateral sensorimotor cortex activation with active and passive hand movement are shown in Figure 6.3, Figure 6.4 and Figure 6.5. Five volunteers demonstrated ipsilateral as well as contralateral sensorimotor cortex activation on active movement of the hand. In all cases, the ipsilateral activation was similar in location to that activated contralaterally on movement of the other hand. With passive movement, however, none of the volunteers showed ipsilateral sensorimotor cortex activation (for example see Figure 6.4). In the majority of cases, active movement produced a greater percentage signal change in the contralateral sensorimotor cortex than passive movement; this difference approached statistical significance ($p=0.07$, paired t-test).

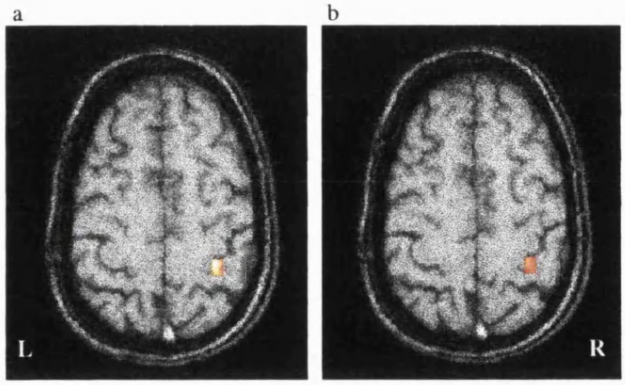


Figure 6.3: Subject 1. Contralateral sensorimotor cortex fMRI activation on active movement (a) and passive movement (b) of the left hand.

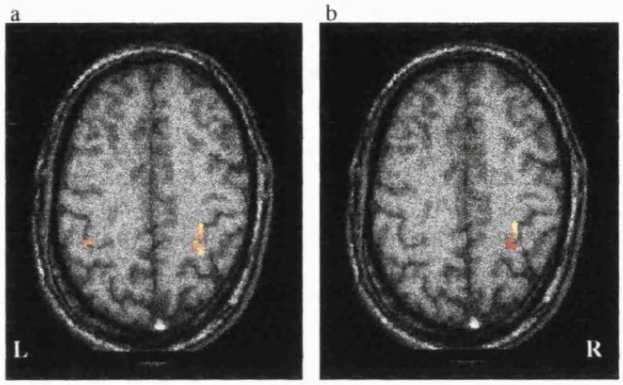


Figure 6.4: Subject 2. Contralateral sensorimotor cortex fMRI activation on active movement (a) and passive movement (b) of the left hand. Note the additional presence of ipsilateral (left sensorimotor cortex) activation with active movement; however ipsilateral activation was not observed on passive movement.

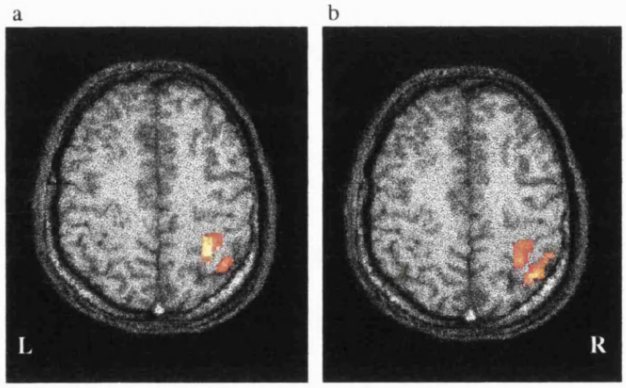


Figure 6.5: Subject 3. Contralateral sensorimotor cortex fMRI activation following active movement (a) and passive movement (b) of the left hand. Note also the presence of posterior 'activation' to that in the central sulcus, most likely due to a lateral draining vessel.

6.3.1.1.2 Left versus right hand active movement

The ten volunteers that were involved in this study are described above (Section 6.3.1.1.1). Examples of results from two left and two right handed volunteers are shown in Figure 6.6 and Figure 6.7. As described above, five of the ten adult volunteers demonstrated ipsilateral as well as normal contralateral sensorimotor cortex activation to an active hand movement task (see Table 6.1). One volunteer (subject 8) showed ipsilateral activation only following active movement of the non-dominant hand, while ipsilateral activation was seen in four volunteers with active movement of both the dominant and non-dominant hand. Both left and right handed volunteers demonstrated ipsilateral activation (3 were left handed, 2 were right handed).

Subject	sex	handedess	right hand movement	left hand movement
1	male	right	c/l	c/l
2	male	right	c/l	c/l
3	female	right	c/l	c/l
4	female	right	c/l + i/l	c/l + i/l
5	female	right	c/l + i/l	c/l + i/l
6	female	right	c/l	c/l
7	male	left	c/l + i/l	c/l + i/l
8	male	left	c/l + i/l	c/l
9	female	left	c/l + i/l	c/l + i/l
10	female	left	c/l	c/l

Table 6.1: Summary of contralateral and ipsilateral sensorimotor cortex fMRI activation following active movement of the left and right hand in 10 adult volunteers of left and right handedness. (c/l=contralateral activation; i/l=ipsilateral activation).

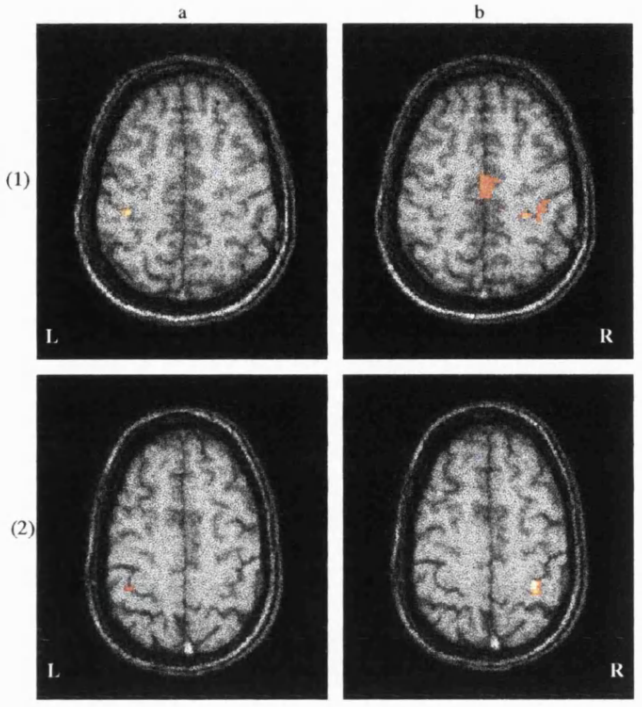


Figure 6.6: Examples of contralateral sensorimotor cortex fMRI activation from two right handed subjects (1=subject 3) and (2=subject 5) performing right (a) and left (b) hand active movement tasks. The SMA shows activation in subject 3 on active movement of the non-dominant hand only.

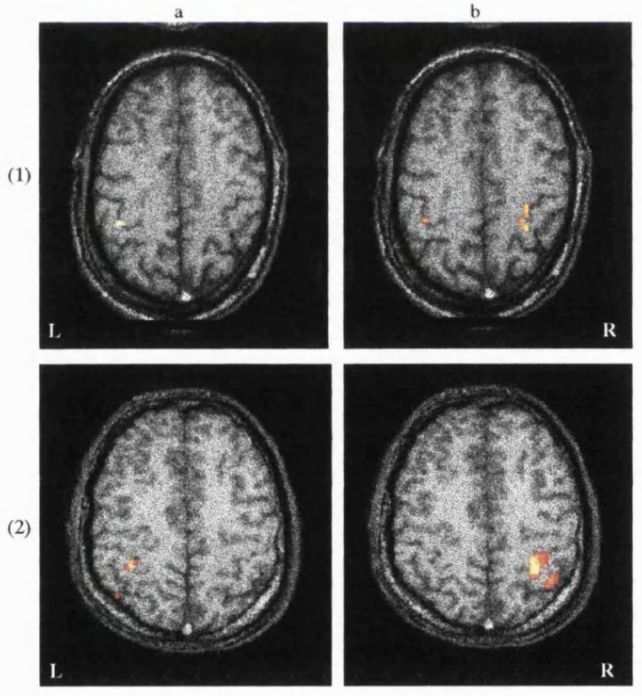


Figure 6.7: Examples of contralateral sensorimotor cortex fMRI activation from two left handed subjects (1=subject 7) and (2=subject 8) performing right (a) and left (b) hand active movement tasks. Note subject 7 also demonstrates ipsilateral sensorimotor cortex activation with active movement of the dominant (and to a lesser extent from the non-dominant) hand. Activation posterior to that in the central sulcus can be seen on movement of the dominant left hand in subject 8, most likely due to venous drainage within a lateral vessel.

6.3.1.1.3 fMRI with electrical stimulation

A total of 14 adult volunteers underwent fMRI with electrical stimulation of the median nerve. In three volunteers, the experiment was repeated in two separate sessions to investigate the reproducibility of the results. Eleven volunteers demonstrated contralateral primary sensorimotor cortex activation, which was similar in location to that seen with active thumb/hand movement (for a typical example see Figure 6.8). None of the volunteers showed ipsilateral activation on electrical stimulation. Two of the three volunteers who were investigated on two separate occasions showed sensorimotor fMRI activation on electrical stimulation that was reproducible between sessions (for example Figure 6.9); the second dataset of the third volunteer was heavily artefacted and could not be corrected using the realignment algorithm in SPM, and so was rejected from the study.

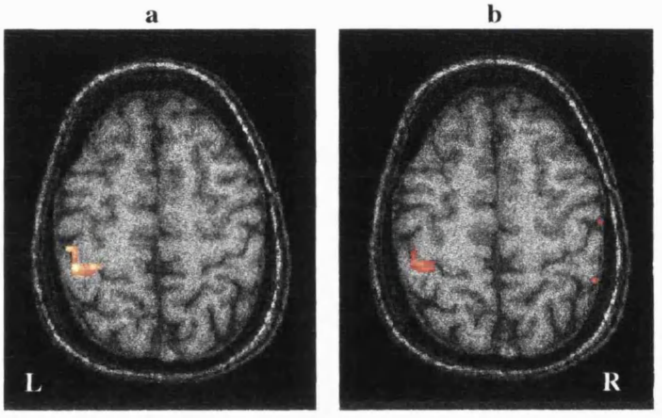


Figure 6.8: Contralateral sensorimotor fMRI activation on right thumb opposition (a) and electrical stimulation of the right median nerve (b) in one volunteer.

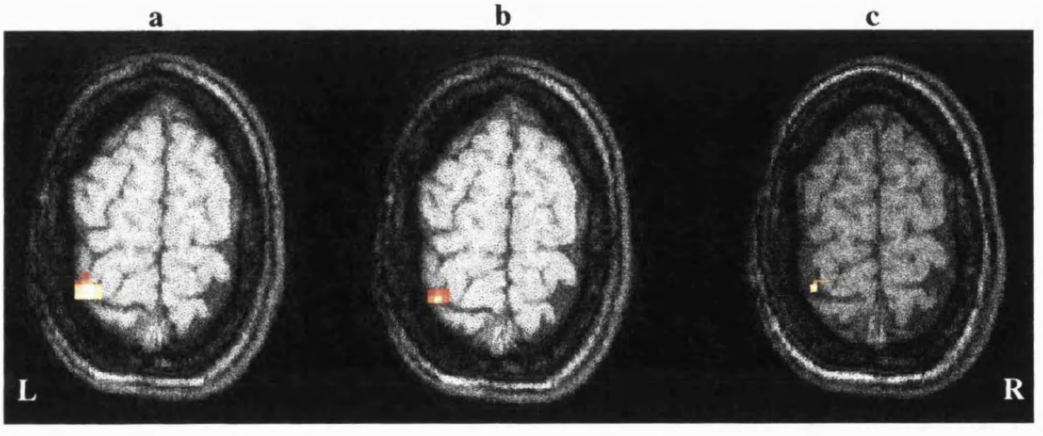


Figure 6.9: Contralateral sensorimotor fMRI activation on right thumb opposition (a) and electrical stimulation of the right median nerve in two separate sessions (b and c) in one volunteer.

6.3.1.2 SEPs

The results of the controls are presented in a similar layout. Waveforms of the peak contralateral (c/l, shaded blue) and ipsilateral (i/l, shaded red) activity are shown, from stimulation of the dominant and non-dominant hands. In addition, 2-D topographical voltage maps for specific time points (comparable early components) from stimulation of each hand are presented.

6.3.1.2.1 Comparison between left and right median nerve electrical stimulation

Ten normal adult subjects were included in the study (refer to Section 6.3.1.1.2 for description of the subjects and their handedness scores). All volunteers demonstrated reproducible contralateral SEP responses following electrical median nerve stimulation of their dominant and non-dominant side. Computed topographical voltage maps indicated that in all cases this response was unilateral and focally located in the region of the primary sensorimotor cortex contralateral to the side of the stimulus. Despite this focal unilateral response seen in the voltage maps, however, small low amplitude responses could also be seen in the waveforms located ipsilateral to the stimulus. The SEP recordings following electrical stimulation are shown in Figure 6.10 and Figure 6.11. Figure 6.10 shows the SEP waveforms and maps in a subject who is strongly right handed (subject 4), while Figure 6.11 demonstrates the results in a strongly left handed volunteer (subject 9).

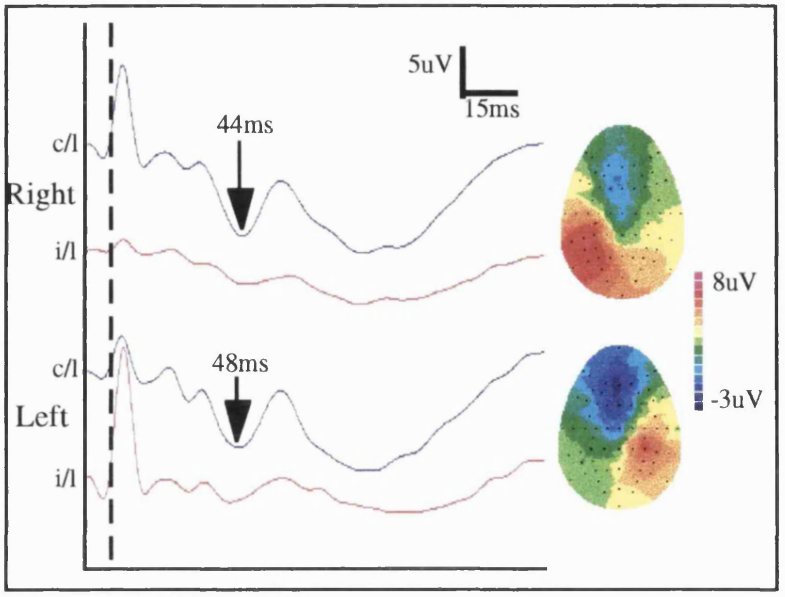


Figure 6.10: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following electrical stimulation of the median nerve of the dominant (right) and non-dominant (left) hand in a strongly right handed subject (subject 4).

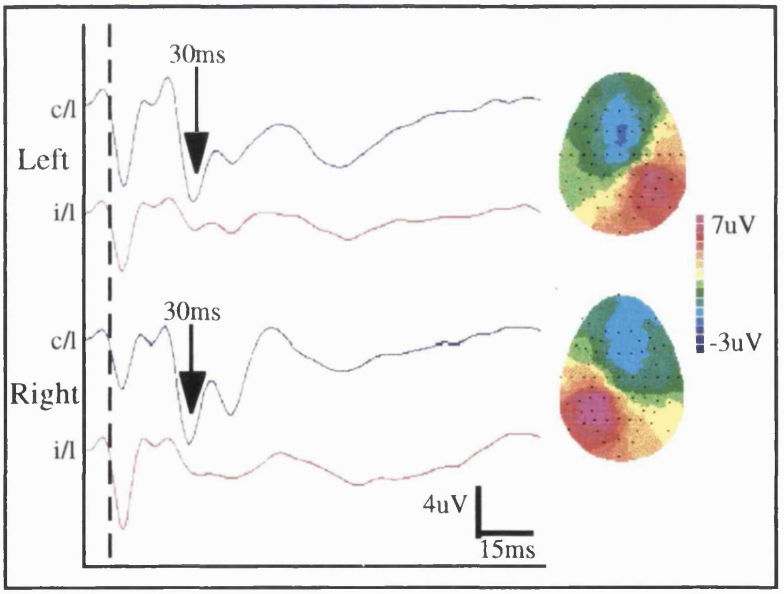


Figure 6.11: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following electrical stimulation of the median nerve of the dominant (left) and non-dominant (right) hand in a strongly left handed subject (subject 9).

Table 6.2 gives the results of amplitude and latency measurements taken from the first positive and negative component in the contralateral and ipsilateral electrode site in right handed volunteers following left and right sided stimulation. Table 6.3 reports the measurements obtained similarly for the group of left handed volunteers.

	Stimulation of dominant side			Stimulation of non-dominant side		
	N20 latency (ms)	P30 latency (ms)	N20/P30 amplitude (μV)	N20 latency (ms)	P30 latency (ms)	N20/P30 amplitude (μV)
c/l response (±standard deviation)	18.2 ±1.7	26.5 ±3.9	3.0±2.3	20.0 ±1.9	27.6 ±6.2	2.5±1.9
i/l response (±standard deviation)	22.4 ±4.3	29.6 ±5.0	1.0±0.7	22.8 ±2.1	33.0 ±3.7	1.6±0.7

Table 6.2: Electrical SEP data from six right handed volunteers: Early components present in the SEP in electrode contralateral (c/l) and ipsilateral (i/l) to the stimulus following electrical stimulation of the median nerve of the dominant and non-dominant side.

	Stimulation of dominant side			Stimulation of non-dominant side		
	N20 latency (ms)	P30 latency (ms)	N20/P30 amplitude (μV)	N20 latency (ms)	P30 latency (ms)	N20/P30 amplitude (μV)
c/l response (±standard deviation)	18.9 ±1.6	28.8 ±1.8	6.3±2.5	19.6 ±1.8	28.3 ±1.8	5.0±2.5
i/l response (±standard deviation)	20.7 ±2.5	30.1 ±2.1	1.8±1.1	21.0 ±2.6	29.8 ±2.2	1.6±0.7

Table 6.3: Electrical SEP data from four left handed volunteers: Early components present in the SEP in electrode contralateral (c/l) and ipsilateral (i/l) to the stimulus following electrical stimulation of the median nerve of the dominant and non-dominant side.

The N20 and P30 ipsilateral responses to electrical stimulation were significantly longer in latency compared to the contralateral measurements in both right and left handed subjects (right handed paired t-tests: N20 $p<0.005$, P30 $p<0.05$; left handed paired t-tests: N20 $p<0.01$, P30 $p<0.05$). The amplitude of the N20/P30 component was also significantly smaller in recordings from the ipsilateral hemisphere compared to the hemisphere contralateral to the side of the stimulus (right handed paired t-test: $p<0.05$; left handed paired t-test: $p<0.0005$).

There was no significant difference between the latency or amplitude of responses on stimulation of the dominant side compared to the non-dominant side ($p>0.05$ for all paired t-test comparisons).

6.3.1.2.2 Comparison between left and right vibrational stimulation

As reported for SEPs in response to electrical stimulation, vibration stimuli produced reproducible contralateral early SEP potentials with stimulation of both the dominant and non-dominant sides. The response was focally located over the region of the contralateral primary sensorimotor cortex in all cases in the topographical voltage maps. Small responses of low amplitude could also be seen in waveforms over the ipsilateral sensorimotor cortex electrodes. The recordings of typical SEPs following vibrational stimulation of the left and right index and middle finger in two of the control subjects are shown in Figure 6.12 and Figure 6.13. Figure 6.12 shows the SEP waveforms and maps in a subject who is strongly right handed and, for comparison, Figure 6.13 demonstrates the results in a strongly left handed volunteer.

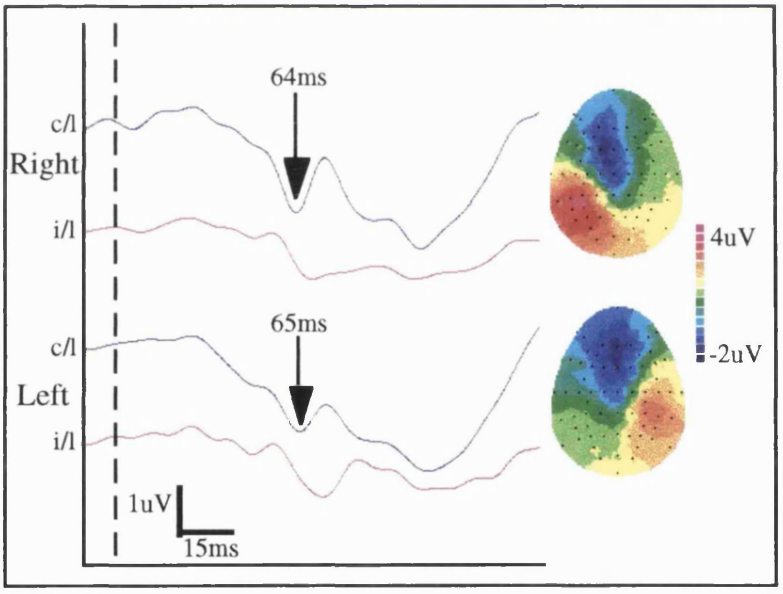


Figure 6.12: SEPs and topographical voltage maps recorded in symmetrical electrodes positioned over the sensorimotor cortex contralateral (c/l) and ipsilateral (i/l) to the side of the stimulus on vibrational stimulation of the dominant (right) and non-dominant (left) index and middle finger in a strongly right handed subject (subject 4).

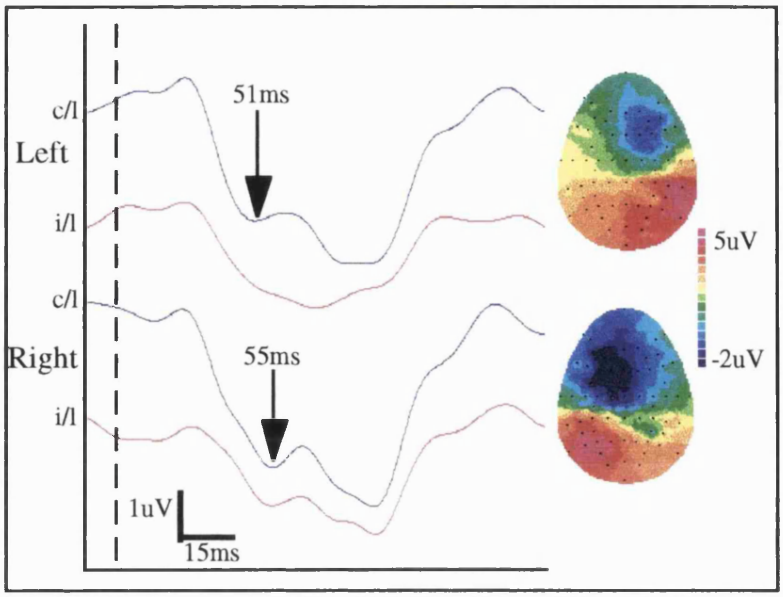


Figure 6.13: SEPs and topographical voltage maps recorded in symmetrical electrodes positioned over the sensorimotor cortex contralateral (c/l) and ipsilateral (i/l) to the side of the stimulus on vibrational stimulation of the dominant (left) and non-dominant (right) index and middle finger in a strongly left handed subject (subject 10).

The results of early latency cortical measurements taken from a contralateral and ipsilateral electrode site in right handed volunteers on left and right sided vibrational stimulation are given in Table 6.4. Table 6.5 reports the equivalent measurements for the group of left handed volunteers.

	Stimulation of dominant side			Stimulation of non-dominant side		
	N30 latency (ms)	P60 latency (ms)	N30/P60 amplitude (μV)	N30 latency (ms)	P60 latency (ms)	N30/P60 amplitude (μV)
c/l response (±standard deviation)	30.5 ±5.8	60.2 ±3.3	2.5±1.0	31.4 ±6.6	65.2 ±4.9	2.5±1.2
i/l response (±standard deviation)	37.7 ±12.4	73.5 ±10.4	1.6±1.1	38.5 ±9.4	70.4 ±3.3	2.1±1.0

Table 6.4: Vibrational SEP data from six right handed volunteers: Early components present in the SEP in electrode contralateral (c/l) and ipsilateral (i/l) to the stimulus following vibrational stimulation of the index and middle finger of the dominant and non-dominant side.

	Stimulation of dominant side			Stimulation of non-dominant side		
	N30 latency (ms)	P60 latency (ms)	N30/P60 amplitude (μV)	N30 latency (ms)	P60 latency (ms)	N30/P60 amplitude (μV)
c/l response (±standard deviation)	30.7 ±6.7	58.6 ±6.0	2.7±1.0	27.8 ±3.8	59.3 ±3.1	3.9±1.9
i/l response (±standard deviation)	35.3 ±7.2	69.3 ±4.6	1.6±1.1	31.9 ±6.2	63.6 ±5.4	1.8±0.5

Table 6.5: Vibrational SEP data from four left handed volunteers: Early components present in the SEP in electrode contralateral (c/l) and ipsilateral (i/l) to the stimulus following vibrational stimulation of the index and middle finger of the dominant and non-dominant side.

Regardless of the side stimulated or the handedness of the subject, the latency of the early components following vibrational stimulation was significantly longer over the ipsilateral hemisphere compared to the contralateral hemisphere (right handed paired t-tests: N30 $p<0.05$, P60 $p<0.01$; left handed paired t-tests: N30 $p<0.05$, P60 $p<0.05$). In addition, the amplitude of this early component was significantly smaller in the ipsilateral hemisphere compared to recordings from the contralateral hemisphere (right handed paired t-test: $p<0.05$; left handed paired t-test: $p<0.01$).

There was no significant difference between the latency or amplitude of responses on stimulation of the dominant compared to non-dominant side ($p>0.05$ for all paired t-test comparisons).

6.3.2 Child controls

Behavioural data were obtained from 7 child controls (1 female, 6 males, age range 9-15, mean 11.9 years). All 7 volunteers underwent electrical SEP recordings, and 5 also underwent vibrational SEPs. Six subjects participated in fMRI investigations of handedness. All of the children were healthy, with no neurological disease.

6.3.2.1 Behavioural Tests

6.3.2.1.1 Handedness

Of the 7 child controls investigated, 4 were right handed (range of scores on the handedness questionnaire 23-29, mean 24.3) and 3 were ambidextrous (range of scores on the handedness questionnaire 32-46, mean 37.7). The individual scores lie within the boundary values for right (18-30) and ambidextrous (31-55), as proposed by Crovitz & Zenner (1962).

6.3.2.1.2 Motor tests

All of the four motor tests (tapping, force production, peg sorting and mirror movements) were carried out in the child controls (as detailed in Chapter 5). The results of the motor tests and the children's handedness assessment are shown in Table 6.6.

Control	Age /sex	Handedness	Tapping	Force production	Peg sorting	Mirror movements?
1 (OB)	11 M	Right	L=115 R=120	L=11.8 R=13.6	L=10.4 R=10.8	No
2 (SM)	15 F	Right	L=83.5 R=100	L=27.8 R=31.2	L=9.1 R=10	No
3 (RD)	13 M	Right	L=79.5 R=92	L=26.1 R=25.3	L=9.9 R=8.9	No
4 (SJ)	9 M	Right	L=90.3 R=92.5	L=18.5 R=20.3	L=12.2 R=10.2	No
5 (AM)	13 M	Ambidextrous	L=86 R=90.5	L=21.5 R=24	L=11.3 R=9.9	No
6 (PN)	10 M	Ambidextrous	L=71 R=90	L=18.2 R=21.2	L=11.9 R=10.2	No
7 (AJ)	12 M	Ambidextrous	L=77 R=89	L=23.8 R=26.7	L=11.1 R=9.6	No

Table 6.6: Results of the motor tests and the children's handedness. Age is in years, M=male, F=female. The test results are listed in the following units: tapping=number per 20 seconds, force production=kg, peg sorting=seconds

Summary of table

There appears to be no difference between the left and right hand scores in relation to handedness; however, the handedness score of the majority of the ambidextrous group bordered the level for right handedness. No mirror movements were observed in either hand in any of the children.

6.3.2.1.3 Sensory tests

Both sensory tests (double simultaneous stimulation of the hand and joint position sense) were carried out in the child controls (as detailed in Chapter 5). The results of the sensory tests and the children's handedness are shown in Table 6.7.

Control	Age /sex	Handedness	Double sim.stim -hand	Position sense
1 (OB)	11 M	Right	L=100 R=100	L=100 R=100
2 (SM)	15 F	Right	L=100 R=100	L=100 R=100
3 (RD)	13 M	Right	L=100 R=100	L=100 R=100
4 (SJ)	9 M	Right	L=89 R=100	L=100 R=100
5 (AM)	13 M	Ambidextrous	L=100 R=100	L=100 R=100
6 (PN)	10 M	Ambidextrous	L=89 R=100	L=100 R=100
7 (AJ)	12 M	Ambidextrous	L=100 R=100	L=100 R=100

Table 6.7: Results of the sensory tests and the children's handedness. Test results are given as percent of responses correct. M=male, F=female (Double sim. stim. - hand = double simultaneous stimulation to the hand).

Summary of table

Regardless of handedness and age, all child controls performed well in the sensory tests. There were no obvious differences on any of the tests between the dominant and non-dominant hand.

6.3.2.2 fMRI

Six of the seven children underwent fMRI investigations. All of the children performed a passive movement task in order to investigated the use of the task in younger subjects, compared to adults. Five children performed passive movement of the left and right hand (subjects 2, 4, 5, 6, and 7), and one volunteer performed passive and active movement of his dominant (right) hand (subject 1). The data from two of the five subjects completing left and right passive tasks did not show any activation in the contralateral primary sensorimotor cortex (subjects 2 and 6). The remaining three child controls (subjects 4, 5 and 7) demonstrated contralateral primary sensorimotor cortex activation with passive movement of either hand, with no ipsilateral sensorimotor cortex activation present (for example see Figure 6.14). This is consistent with the fMRI findings for passive movement in adult control subjects reported in Section 6.3.1.1.2. In the child who performed active and passive movement of the dominant hand, both studies showed only contralateral sensorimotor cortex activation which was similar in location for the two tasks (Figure 6.15).

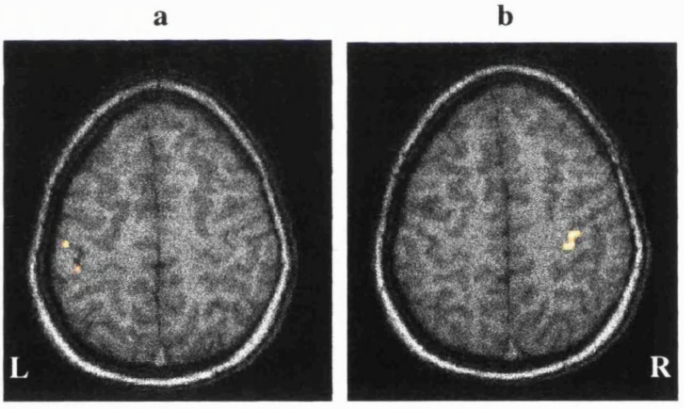


Figure 6.14: Contralateral sensorimotor cortex fMRI activation on right (a) and left (b) passive movement of the hand in one child volunteer (subject 4).

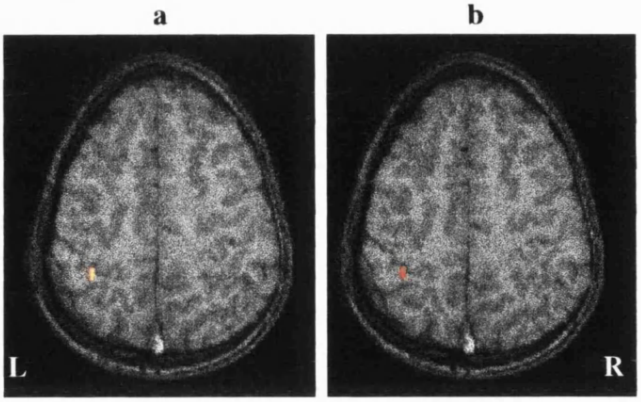


Figure 6.15: Comparative contralateral sensorimotor cortex fMRI activation on active (a) and passive (b) movement of the right (dominant) hand in one child volunteer (subject 1).

6.3.2.3 SEPs

The results of the patients are presented in a similar layout. Waveforms of the peak contralateral (c/l, shaded blue) and ipsilateral (i/l, shaded red) activity are shown, from stimulation of the dominant and non-dominant side. In addition, 2-D topographical voltage maps for specific time points (comparable early components) from stimulation of each side are presented.

6.3.2.3.1 Comparison between left and right median nerve electrical stimulation

All 7 child controls demonstrated reproducible contralateral SEP responses on electrical stimulation of the median nerve. The response was, in all cases, maximal in amplitude over the contralateral sensorimotor cortex, as seen in the topographical voltage maps. The contralateral and ipsilateral SEP recordings on electrical stimulation of the left and right median nerve in two of the control subjects are shown in Figure 6.16 and Figure 6.17. In three subjects of either right or ambidextrous handedness (numbered 2, 3, and 7), SEP potentials could also be seen in waveforms ipsilateral to the side of the stimulus, but these were smaller in amplitude compared to the contralateral potentials (for example see Figure 6.17).

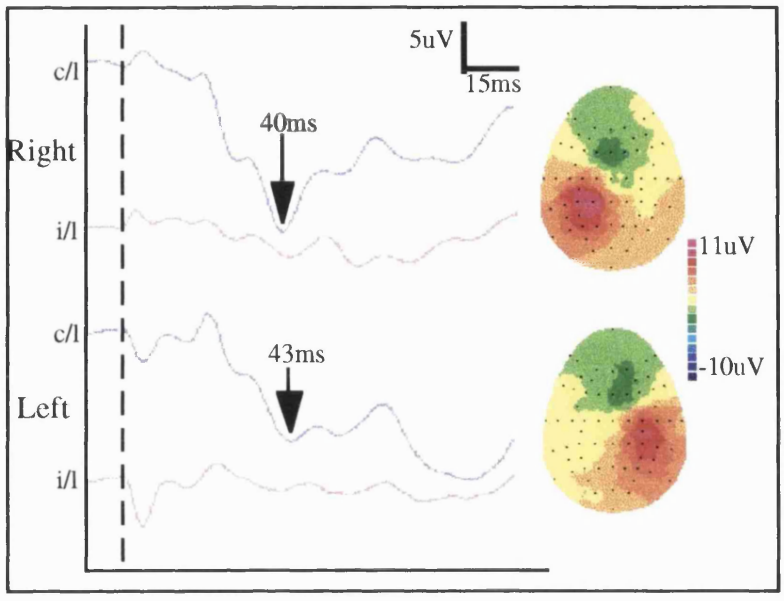


Figure 6.16: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following electrical stimulation of the median nerve of the dominant (right) and non-dominant (left) hand in a child control (subject 5).

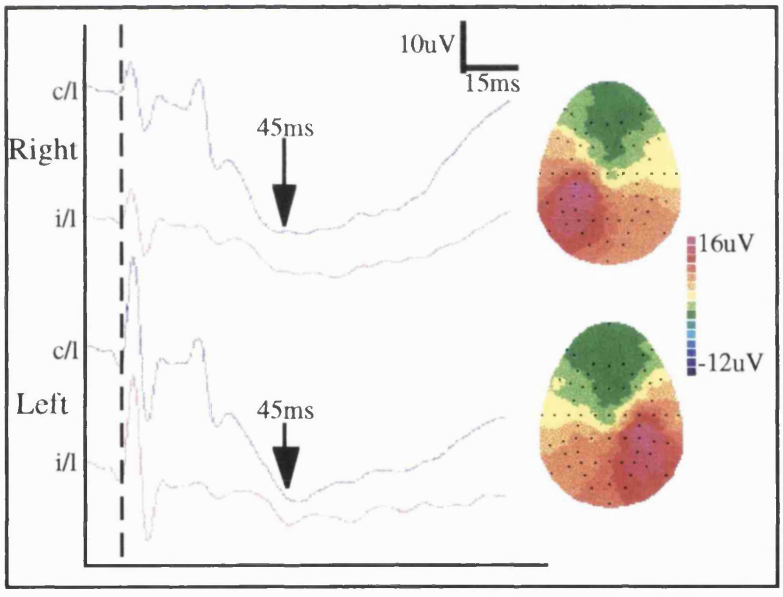


Figure 6.17: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following electrical stimulation of the median nerve of the right and left hand in a child control (subject 7).

6.3.2.3.2 Comparison between left and right index and middle finger vibrational stimulation

SEPs in response to vibration stimuli were obtained in 5 of the 7 child controls in the study (subjects 2, 4, 5, 6, 7). The results were similar to those obtained with electrical stimulation. All 5 subjects demonstrated focal contralateral SEP responses following vibrational stimulation which were maximal in amplitude over the sensorimotor cortex as seen in the voltage maps. In addition, the waveforms of three of the subjects showed SEP responses in electrodes located ipsilateral to the side of the stimulus (subjects 3, 5, and 7). In each case, these ipsilateral responses were smaller in amplitude than the contralateral response (for example see Figure 6.19). The contralateral and ipsilateral SEP recordings following vibrational stimulation of the left and right index and middle finger in two of the control subjects are shown in Figure 6.18 and Figure 6.19.

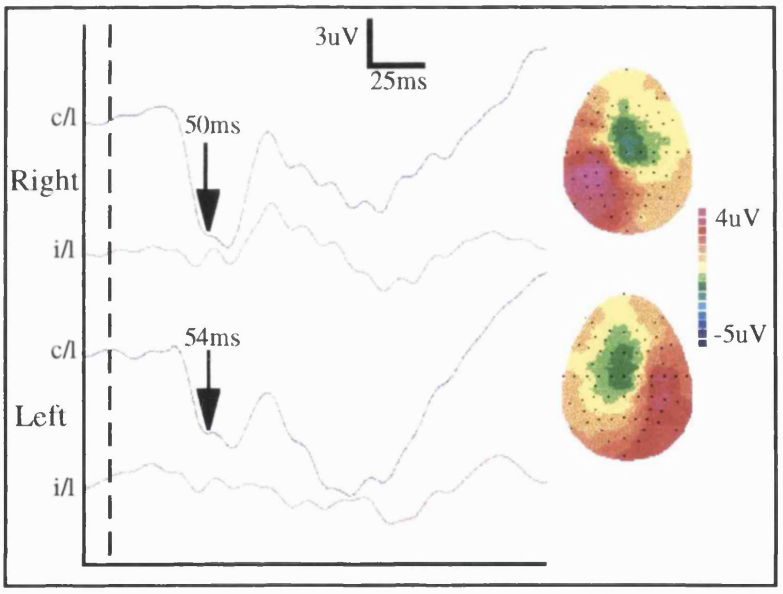


Figure 6.18: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following vibrational stimulation of the index and middle finger of the dominant (right) and non-dominant (left) hand in a child control (subject 4).

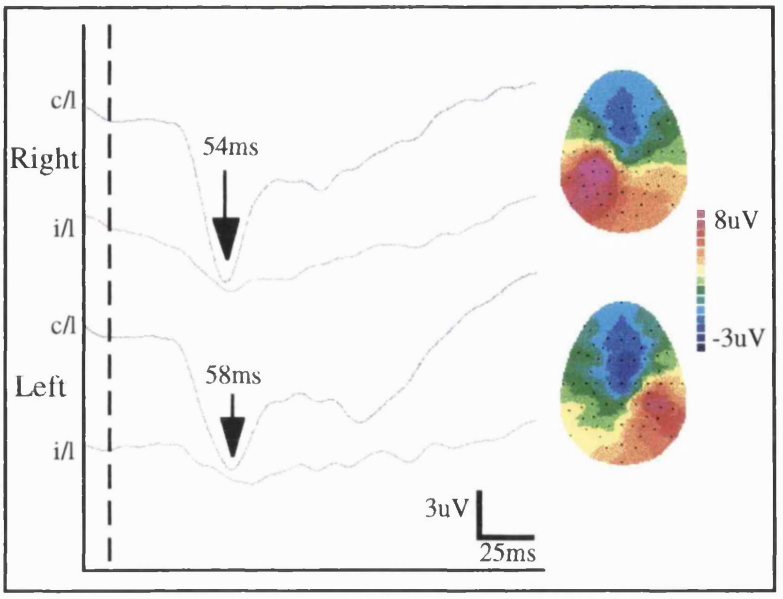


Figure 6.19: SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus over the sensorimotor cortex following vibrational stimulation of the index and middle finger of the right and left hand in a child control (subject 7).

6.3.3 Summary of adult and child control data

Normal contralateral sensorimotor cortex fMRI activation was seen in the adult controls and four out of six child controls with a passive and/or active hand motor task. Five out of ten adult volunteers also demonstrated ipsilateral fMRI sensorimotor cortex activation with active movement of the hand, but this was not seen in any of the subjects with a passive movement task. Similarly, none of the child control subjects showed ipsilateral activation with passive movement. With SEPs, normal contralateral responses were recorded in all of the adult and child controls to electrical and/or vibrational stimulation. None of the adult or child controls demonstrated isolated focal ipsilateral responses in topographical voltage maps. Ipsilateral potentials, however, were evident in waveforms; these were smaller in amplitude and longer in latency than the contralateral response.

6.4 Discussion

In this study, fMRI and SEP methods have been investigated for their reliability in detecting activation of the primary sensorimotor cortex. The paradigms used in this study were specifically chosen and developed for use in patients who have hand sensorimotor deficits, and would involve little co-operation from younger or intellectually impaired children. Three tasks have been shown to demonstrate activation of the contralateral primary sensorimotor cortex on fMRI, namely active movement,

passive movement and electrical stimulation. Electrical and vibration stimuli have both been shown to demonstrate reliable activation of the contralateral primary sensorimotor area on SEP recordings. Studies were carried out in adult and child controls. In both groups of subjects, no difference was seen in the location of contralateral responses obtained using fMRI or SEP recordings.

Variability in the number, the level of significance, and the extent of activated regions was seen between the control subjects over the different tasks performed. Some volunteers showed activation maps with several sensorimotor areas activated (for example contralateral and ipsilateral primary sensorimotor areas, SMA), and were of high significance. Other volunteers did not show activation as readily in the sensorimotor areas, with only a small region of activation of low significance in the contralateral primary sensorimotor area. With passive movement and electrical stimulation, most volunteers demonstrated activation in the contralateral sensorimotor area; however, some volunteers did not show any activation with these tasks. Examination of the realignment graphs (see Section 3.2.1.1 of Chapter 3) did not show a difference in the amount of movement between these control subjects. There is no obvious reason for the difference in the activation maps between these subjects. These data appear to support the results of the reproducibility experiment described in Section 3.5 of Chapter 3, which showed that there is a large variation in the percentage signal change on repeated measures in any individual volunteer. This study has also suggested that passive movement is less sensitive in producing fMRI activation in the primary sensorimotor cortex compared to an active movement task.

Ipsilateral fMRI activation was seen only with active movement of the hand in adult controls; there was no evidence of such ipsilateral responses with passive movement or electrical stimulation tasks in either adults or children. In both adult and child controls, focal contralateral SEP responses were seen on constructed voltage maps of early latency components. Although there is previous evidence in the literature to suggest that ipsilateral connections may be more prevalent in young children (see Section 1.5 of Chapter 1) this was not shown with the methods used with normal volunteers in this study. However, the youngest child studied was 9 years old, which is around the age at which it has been suggested that neuronal maturity occurs and transcallosal inhibition is established (Muller et al. 1997a). Several previous studies in normal controls have demonstrated the presence of ipsilateral sensorimotor responses using a variety of techniques, including PET (Shibasaki et al. 1993; Remy et al. 1994; Sadato et al. 1996a), TMS (Wassermann et al. 1991, 1994; Chen et al. 1997a&b), MEG (Korvenoja

et al. 1995; Hoshiyama et al. 1997), and SPECT (Sabatini et al. 1993). The implication and underlying mechanisms of these ipsilateral responses are discussed below.

6.4.1 Ipsilateral primary sensorimotor cortex responses detected in normal controls using fMRI

In this study, ipsilateral primary sensorimotor cortex activation was seen in addition to contralateral activation in half of the adult volunteers (5 out of 10) who carried out an active hand motor task. None of the volunteers demonstrated ipsilateral activation in the absence of contralateral activation. During a comparable passive movement task of the same hand, only contralateral activation was demonstrated in all of the adults involved in the study. There have been reports in the literature of ipsilateral sensorimotor activation in addition to contralateral activation using fMRI (for a review of the studies see Sections 2.3.1.1 and 2.3.2 of Chapters 2). In agreement with the findings of this study, all of these studies have involved using an active motor task, in particular a complex as opposed to a simple motor task (for example Rao et al. 1993). In the few studies that have investigated passive movement as a method of activating the sensorimotor cortex, there have been no reports of ipsilateral activation in addition to contralateral primary sensorimotor cortex activation (such as Bernard et al. 1996; Krams et al. 1997). In particular, Goran et al. (1996) reported ipsilateral primary motor cortex activation in 2 out of 4 subjects performing an active foot flexion task; however no ipsilateral activation was detected with a passive task in any of the subjects. In the present study, electrical stimulation was found to be a reliable task for activating the contralateral sensorimotor cortex in 11 out of 14 of subjects using fMRI, none of the volunteers demonstrating ipsilateral activation with the task. The majority of the literature supports this finding of predominantly contralateral primary sensory and motor cortex activation with electrical stimulation in fMRI (for example Schreiber et al. 1997; Grimm et al. 1998; Spiegel et al. 1999). Two studies have observed ipsilateral primary sensorimotor cortex activation (Korvenoja et al. 1996; Villringer et al. 1997). However, this ipsilateral activation was reported to be smaller in spatial extent compared to contralateral activation (Korvenoja et al. 1996).

There have been numerous studies carried out in subjects of left and right hand dominance to investigate activation of the sensorimotor areas using fMRI. A review of these studies is presented in Section 2.3.2 of Chapter 2. In right handed subjects, ipsilateral primary sensorimotor cortex activation has most often been demonstrated with active movement of the non-dominant (left) hand (for example Li et al. 1996). In

contrast, one study with right handed subjects demonstrated both contralateral and ipsilateral activation of the primary motor cortex following movement of the left and right hand (Roth et al. 1996). In left handed subjects, however, there has been reported to be no significant difference in the pattern of sensorimotor cortex activation, with contralateral and ipsilateral activation seen following movement of either hand (Falk et al. 1997). In all studies, the size of any ipsilaterally activated region was smaller than that of the corresponding contralateral activation (for example Singh et al. 1998a). In this study, no relationship was found between the presence of ipsilateral activation on active movement of the dominant or non-dominant hand in subjects of left or right handedness. This is in agreement with the findings of Roth et al. (1996) with right handed subjects, and with Falk et al. (1997) in left handed subjects, described above. As only a small number of subjects were included in the present study, however, the results should be interpreted with caution. In order to substantiate these findings, a greater number of subjects would need to be studied.

It has been reported that the ipsilateral activated region in the sensorimotor area lies anterior to the peak location of contralateral activation (Sadato et al. 1996a; Singh et al. 1998a; see Section 2.3.1.1 of Chapter 2). This may represent either a real shift in the representation of the ipsilateral sensorimotor cortex (Wassermann et al. 1994) or may be due to the absence of sensory feedback on the ipsilateral side (Sadato et al. 1996a). In contrast, Kim et al. (1993b) showed ipsilateral activation located in a similar region to the site of contralateral activation within the primary sensorimotor cortices. The present study supports the findings from Kim et al. (1993b), showing no difference in the peak location of the ipsilateral compared to comparable contralateral activation with an active hand motor task using fMRI.

6.4.2 Ipsilateral responses in the region of the primary sensorimotor cortex in normal controls using SEP recordings

This study has demonstrated that short latency SEPs following median nerve stimulation show the highest amplitude on the contralateral centro-parietal scalp, in the region of the primary sensorimotor cortex. Indeed, both invasive and non-invasive SEP studies have supported the notion that the cortical generators of the early SEP components are located in the contralateral sensorimotor cortex (for a review of the literature, refer to Section 4.4.1 of Chapter 4). In addition to contralateral responses, ipsilateral SEP responses were evident in the waveforms recorded following both electrical and vibration stimuli. The ipsilateral components were similar in topography to those of their contralateral

counterparts; however in all cases, the early components were comparatively smaller in amplitude and longer in latency. In contrast, when the first positive component (the P30 and P40 for electrical and vibration stimuli, respectively) in the present study was displayed as a topographical 2-D voltage map, the response was clearly unilateral and focally located over the contralateral primary sensorimotor area. Neither the left- nor right-handed volunteers showed any evidence of a focal ipsilateral response in the voltage maps on stimulation of their dominant or non-dominant side. In a small number of subjects, the SEP response was observed over both sensorimotor cortices, but the peak response was clearly maximal in amplitude over the contralateral hemisphere.

There have been a number of studies demonstrating the presence of ipsilateral scalp recorded responses in the region of the sensorimotor area in normal humans following unilateral stimulation (Larson et al. 1966; Yamada et al. 1984; Tsuji et al. 1988; Korvenoja et al. 1995). One study suggested that ipsilateral SEP responses recorded from subdural electrodes may reflect unconscious sensory input from the hand, possible serving bimanual hand control (Noachtar et al. 1997), or kinaesthetic or position sense of the ipsilateral hand (Lueders et al. 1985). In the majority of studies, invasive cortical SEP recordings have not detected consistent short latency ipsilateral responses in patients (for example Goldring et al. 1970; Lueders et al. 1983; Wood et al. 1988; Allison et al. 1989a), or animals (Marshall et al. 1941); however there are exceptions, such as Tamura (1972), Aleev & Varezhkin (1978), and Noachtar et al. (1997). Ipsilateral responses have been demonstrated in a small number of the patients evaluated for epilepsy surgery; for example in 1 out of 8 patients (Lueders et al. 1984), 2 out of 15 patients (Lueders et al. 1986), in 2 out of 21 patients (Lueders et al. 1985), and, in an extended study of that of Lueders et al. (1986), in 4 out of 41 patients (Noachtar et al. 1997). In addition, ipsilateral cortical responses of a longer latency than contralateral responses have been recorded in the cat (Nakahama, 1958). It is unclear whether the low incidence of ipsilateral SEPs is because the generators are located deep within the central sulcus and oriented horizontally (so not detectable on the brain surface), or that they occur only in selected patients secondary to reorganisation of the sensorimotor cortex. Noachtar et al. (1997) suggested that such a localised and low amplitude ipsilateral SEP response is unlikely to be detectable by scalp recordings.

There are at least three possible explanations for the presence of ipsilateral, in addition to contralateral, SEP responses in the recorded waveforms:

1. It has been proposed that in animals ipsilateral SEPs in the sensorimotor cortex are mediated by the corpus callosum from the contralateral hemisphere (Eidelbarg &

Jenkins, 1966; Eidelberg, 1969). The same mechanism has also been proposed in man (Williamson et al. 1970; Tamura, 1972; Kuksova & Sumskii, 1983; Kunesch et al. 1995). Innocenti et al. (1974) identified fibres coming from the somatosensory cortex and conducting impulses to the opposite hemisphere in the corpus callosum of the cat. However, the transmission of an electrically or magnetically elicited signal from the somatosensory cortex through the corpus callosum to the contralateral somatosensory cortex requires at least 9 ms (Amassian & Cracco, 1987; Cracco et al. 1989). In the study by Noachtar et al. (1997), the delay between the ipsilateral and contralateral SEP responses was less than 6.3 ms, so it appears extremely unlikely that the ipsilateral responses that they reported were transmitted through the corpus callosum. Similarly, it seems unlikely that this mechanism underlies the delay seen following electrical stimuli in the present study (approximately 2-4 ms). In addition, Larson et al. (1966) noted that the progressively decreasing amplitude with increasing distance from the area of maximum contralateral amplitude on the scalp recorded electrodes also makes the proposed mechanism unlikely.

2. Ipsilateral SEP responses may arise as a result of volume conduction of the responses from the contralateral side over the surface of the scalp (Kakigi, 1986). The more common absence of ipsilateral responses in cortical recordings compared to a higher incidence of scalp recorded ipsilateral responses in the majority of studies makes the callosally-mediated response less likely. By implication this suggests that volume conduction (Larson et al. 1966; Lueders et al. 1983) or a 'smearing' effect from a generator located within the rolandic fissure and sensorimotor cortex (Tsuji et al. 1988) is a more likely mechanism for the presence of ipsilateral responses. This is supported by the fact that ipsilateral components show similar latencies to their contralateral counterparts and that with more distant recording sites there is a gradual fall off in amplitude of the potential (Larson et al. 1966; Kakigi, 1986). This hypothesis is supported in this study by the results of the voltage maps showing that contralateral peak components occasionally spread over the ipsilateral hemisphere, but that no peak SEP responses are located over the ipsilateral sensorimotor cortex.

3. Uncrossed afferent fibres have been found to project to the ipsilateral sensorimotor cortex (see Sections 1.3.4.1 and 1.4.3.3 of Chapter 1) and may be the mechanism behind ipsilateral SEP responses. Based on the distance from the wrist to the sensorimotor cortex of approximately 110 cm, a conduction velocity of at least 40 m/sec is needed to explain the latency delay of 5-6 ms in responses recorded invasively (Noachtar et al. 1997). Previous literature indicates that ipsilateral afferent pathways such as the spinothalamic pathway may not be fast enough (Kakigi & Shibasaki, 1991).

However, Aleev & Varezhkin (1978) noted that if such pathways were responsible for ipsilateral SEP responses, there would be no expected difference in the latency or amplitude compared to contralateral responses. It has been shown, however, that in patients who have undergone hemispherectomy and have no interference from the contralateral hemisphere, ipsilateral responses can be recorded on stimulation of the hemiplegic hand which are longer in latency and smaller in amplitude compared to the normal contralateral response (Villanueva & Castilla, 1988; see Section 7.1.4.1 of Chapter 7). This suggests the presence of ipsilateral pathways with a longer conduction time than normal contralateral pathways in patients with such brain damage.

Chapter 7: Reorganisation of sensorimotor function in patients with hemispherectomy

7.1 Introduction

7.1.1 Aims of this study

The aims of this study are three-fold: firstly, to use fMRI and SEP techniques in a group of hemispherectomised children to attempt to identify and locate the cortical substrate for residual sensorimotor function contralateral to the hemispherectomised side; secondly, to determine using behavioural measures the extent of residual sensory and motor function in the distal portion of the upper limb contralateral to the hemispherectomised side, and to relate the findings to the fMRI and SEP data; finally, to compare the findings from all three techniques in patients with congenital disease and those with acquired disease.

7.1.2 Hemispherectomy

Hemispherectomy is a surgical procedure that is sometimes performed for the treatment of patients with severe drug-resistant epilepsy arising from conditions such as hemimegalencephaly, Sturge-Weber syndrome, infantile hemiplegia, and Rasmussen's encephalitis (Meagher-Villemure, 1997). Currently, hemispherectomy provides seizure control in almost 85% of such patients (Peacock et al. 1996).

The current techniques of hemispherectomy are categorised in three major groups: anatomical hemispherectomy, hemidecortication, and functional hemispherectomy (for a detailed review, see Villemure, 1997). Anatomical hemispherectomy involves the disconnection and removal of an entire cerebral hemisphere. The technique, however, has several variations, depending on the removal or preservation of a number of the subcortical structures such as the caudate nucleus, putamen, globus pallidus, amygdala, hippocampus and the insula cortex. A modified version of the standard anatomical hemispherectomy now exists to reduce post-operative complications, called Adams modification (Adams, 1983). Hemidecortication consists of removing the grey matter and preserving white matter, thus not opening the ventricles, with a temporal lobectomy done to facilitate removal of the medial temporal structures. Finally, the functional, or

'subtotal', hemispherectomy has become common as it was found that leaving some tissue in the hemispherectomy cavity seemed to provide protection against certain post-operative complications, in particular superficial cortical haemosiderosis (Rasmussen, 1973; Tinuper et al. 1988; Villemure & Rasmussen, 1993). The procedure consists of the removal of at least three cortical lobes (at least two thirds of the grey and white matter), with portions of the prefrontal and parieto-occipital lobes and subcortical structures left in place, and a complete callosotomy. Complete disconnection of these anterior, posterior and subcortical elements from both the brainstem and opposite hemisphere provides the same physiological results as a complete anatomical hemispherectomy (Villemura & Rasmussen, 1990). In addition, the 'hemispherotomy' is a variation of the functional hemispherectomy, it being the surgical procedure that requires the smallest brain volume removal to accomplish a complete hemispheric disconnection (Villemure & Mascott, 1995). Today only the 'subtotal' hemispherectomy procedures are widely performed in both adult and child cases of epilepsy, with the total anatomical procedure being used only in a small number of cases (Wyllie et al. 1996). Other alternative surgical techniques for hemispherectomy are still being developed (Schramm et al. 1995). The term 'hemispherectomy' is applied to all these surgical procedures in which there is complete functional disconnection of one cerebral hemisphere, which may be totally or partially removed (Villemure, 1997).

7.1.3 Sensory and motor functional outcome after hemispherectomy

Since the initial use of hemispherectomy as a surgical procedure in patients with intractable epilepsy, studies have examined the extent of residual sensorimotor function post-operatively (including Bell & Karnosh, 1949; French & Johnson, 1955a; French & Johnson, 1955b; Ueki, 1966; Zulch & Micheler, 1978; Muller et al. 1991). A number of investigations have noted a remarkable degree of residual sensorimotor function in the limb contralateral to the excised hemisphere (Bell & Karnosh, 1949; Krynauw, 1950; Cairns & Davidson, 1951; French & Johnson, 1955a,b; Obrador, 1964; Ueki, 1966; Wilson, 1970; Zulch, 1974; Zulch & Micheler, 1978; Glees, 1980; Verity et al. 1982; Muller et al. 1991) with some showing unchanged or even improved residual motor function after surgery (Gardner et al. 1955; Damasio et al. 1975; Ameli, 1980; Beardsworth & Adams, 1988; Bare, 1989; Becking et al. 1994; Peacock et al. 1996; Vargha-Khadem et al. 1997). As the entire sensorimotor cortical and subcortical structures in one hemisphere are removed or functionally disconnected in these patients, this residual function must be subserved by the remaining hemisphere.

Most reports have concentrated on sensory and motor impairments on the side contralateral to the removed hemisphere, while ipsilateral sensorimotor impairments have received little attention.

7.1.3.1 Contralesional residual motor function after hemispherectomy

Early studies were divided as to the positive benefits of hemispherectomy with respect to functional motor outcome, with some reporting a high proportion of improved functioning post surgery (White, 1961; Ignelzi & Bucy, 1968); however others did not show an improvement of function (Wilson, 1970). Several studies have noted that motor functioning on the side contralateral to the removed hemisphere is usually more affected in the arm than the leg (Gardner, 1933; Bell & Karnosh, 1949; Zulch, 1974), which in turn is more affected than the face (Gardner et al. 1955; Wilson, 1970; Zulch & Micheler, 1978). The preserved motor function in the lower limb in many cases has been such that the patient can walk (such as Gardner et al. 1955; Ameli, 1980; Verity et al. 1982; Muller et al. 1991; Vargha-Khadem et al. 1997), although not in all cases (Dandy, 1928; Wilson, 1970). Walking has been shown, however, to be controlled at least partly at a subcortical level as well as by the cerebellum (Gamper, 1926; Travis & Woolsey, 1956; Shik & Orlovsky, 1976). Distal lower limb motor functioning (the toes and ankles) is usually more affected and often completely lost (for example Gardner et al. 1955; Verity et al. 1982).

There appears to be a proximal-distal gradient to residual motor functioning in the upper limb also, the hand and wrist function being most affected by the loss of the contralateral sensorimotor cortex (Gardner et al. 1955; Zulch, 1974; Damasio et al. 1975; Muller et al. 1991; Dijkerman, 1996). The proximal part of the limb may even function almost normally according to some studies (Damasio et al. 1975; Verity et al. 1982). Often the patient has enough power in the proximal portion of the contralateral arm to allow it to be of functional use, for example to steady objects (Verity et al. 1982). The degree of residual functioning reported in the contralesional hand has been variable, ranging from being able to pick up a glass (Zulch, 1954; Ueki, 1966; Dijkerman, 1996; Vargha-Khadem et al. 1997), and some individual fine finger movements (French & Johnson, 1955a), to a complete hemiplegia and a useless hand (Dandy, 1928; Wilson, 1970; Dijkerman, 1996). A proximal-distal gradient has also been found in hemiplegic patients, whose damaged hemisphere has not been removed (Brown et al. 1987; Colebatch & Gandevia, 1989; Dijkerman, 1996).

7.1.3.2 Contralesional residual sensory function after hemispherectomy

The distribution of somatosensory residual function in the body is similar to that reported for residual motor function. Specifically, the upper limb sensory function is more affected than the lower limb and face (Obrador, 1964) and a within-limb proximal-distal gradient has also been found for somatosensory function in patients with hemispherectomy (Zulch, 1974; Ameli, 1980; Muller et al. 1991; Dijkerman, 1996).

A variety of behavioural tests, some of which have been used to assess sensory function in patients in this study, have been used by other groups to determine the presence and extent of residual sensory function in hemispherectomised patients. There appears to be a wide variation in the degree of impairment with respect to the different aspects of somatosensory functioning in the upper limb. Two point discrimination of the upper limb is usually impaired but ranges in extent from almost normal (Zulch, 1974; Ameli, 1980), or slightly impaired (Wilson, 1970; Damasio et al. 1975; Knecht et al. 1996), to a complete loss (Gardner et al. 1955). Joint position sense is reported to be often impaired in the fingers and/or wrist but preserved in the elbow and shoulder (Zulch, 1974; Zulch & Micheler, 1978; Ameli, 1980; Muller et al. 1991). Stereognosis is most consistently severely impaired in the contralesional hand of hemispherectomy patients (Gardner et al. 1955; Ameli, 1980; Verity et al. 1982; Muller et al. 1991); however in this test it is difficult to distinguish between a pure sensory deficit and the effect of a motor impairment. Detection of vibration in the hand may vary from a complete loss (Gardner, 1933), to a moderate impairment (Bell & Karnosh, 1949; Zulch, 1974), to even full preservation (French & Johnson, 1955b; Muller et al. 1991; Knecht et al. 1996). Other tests of sensory function (namely graphesthesia, the ability to identify numbers or letters traced on the skin with a blunt object, and temperature sensitivity) also vary in the extent of deficit incurred, from apparently normal function (French & Johnson, 1955b; Zulch & Micheler, 1978; Knecht et al. 1996) to moderate or severe impairment (Gardner, 1933; Ueki, 1966; Damasio et al. 1975; Knecht et al. 1996).

7.1.3.3 Mirror movements

Mirror movements have been defined as '...associated or synkinetic movements that are executed involuntarily by a muscle group or limb on one side of the body in response to an intentionally performed movement in the corresponding contralateral muscle-group limb' (Rasmussen, 1993). In practice they can be easily diagnosed when the subject is asked to move one hand, but involuntary movements of the contralateral hand occur that

are almost symmetrical and simultaneous in pattern. Several studies have shown mirror movements to be a normal phenomenon in children below the age of 10 years (Conolly & Stratton, 1986; Muller et al. 1997a). Their persistence after this first decade of life, or when full maturation of the nervous system is thought to have occurred, is considered abnormal and is quite rare (Schott & Wyke, 1981; Nass, 1985; Rasmussen, 1993). Adult patients with various neurological abnormalities may continue to display mirror movements, particularly if there was an early onset of brain damage or disease (Woods & Teuber, 1978). Several studies have reported mirror movements in patients who have undergone hemispherectomy (Ueki, 1966; Muller et al. 1991; Dijkerman, 1996).

At present, there is no generally accepted explanation of the anatomical and physiological mechanisms underlying persistent mirror movements (Carr et al. 1993). One possible explanation stems from the finding that the disappearance of mirror movements in children coincides with the completion of myelination of the corpus callosum (Yakolev & Lecours, 1967). It is thought that the ipsilateral pathway is responsible for mirror movements in childhood but this pathway gradually comes under inhibitory control of the contralateral hemisphere (through the corpus callosum) (Muller et al. 1997a). At the time of callosal maturation, an impairment may occur which affects the callosally-mediated inhibition of ipsilateral projections originating from the opposite motor cortex. This would result in the simultaneous activation of both motor cortices and consequently adult mirror movements (Schott & Wyke, 1981; Nass, 1985; Forget et al. 1986; Danek et al. 1992; see Section 1.5 of Chapter 1). However, investigations using TMS have generally shown bilateral responses from unilateral stimulation in patients with mirror movements that are of comparable latency (Farmer et al. 1990; Cohen et al. 1991a; Mayston et al. 1997). Because the conduction through the human corpus callosum requires about 9 ms (Amassian & Cracco, 1987), it is unlikely that transcallosal connections are responsible for these bilateral responses after unilateral stimulation. The TMS ipsilateral responses are also unlikely to be due to current spread, as such responses are not recorded in normal patients in identical stimulus paradigms (Cohen & Hallet, 1988). A second theory, but perhaps more likely given the findings in hemispherectomy patients with different ages of onset of disease, is that mirror movements occur as a result of reorganisation of the pyramidal motor system (Farmer et al. 1990; Cohen et al. 1991a; Muller et al. 1991; Mayer et al. 1995; Mayston et al. 1997; Nirkko et al. 1997). In patients with mirror movements, one hemisphere may participate in the direct control of both sides of the body, although at the expense of fully independent unilateral control. Functional PET, MRI, and TMS studies have demonstrated bilateral activations from attempted unilateral movements in patients with mirror movements, and in such cases the ipsilateral response may be greater than in

normal controls (Cohen et al. 1991a; Krams et al. 1997; Leinsinger et al. 1997; Nirkko et al. 1997). These data could be interpreted as being consistent with the hypothesis for the presence of ipsilateral pathways if it supposed that the motor cortex activation contralateral to the mirroring hand is as a result of the mirror movements rather than, for example, sensory feedback (Krams et al. 1997). There is debate in the literature as to whether ipsilateral projections in adulthood are a result of more extensive or enhanced connections of original fibres, or due to novel pathways arising from axonal sprouting (Maegaki et al. 1995; Mayston et al. 1997; Muller et al. 1997a). Whatever the mechanism, it is possible that patients with mirror movements have a greater number of these ipsilateral corticospinal fibres, compared to controls, that are activated in addition to the decussating fibres.

7.1.3.4 Do sensorimotor deficits occur in the side of the body ipsilateral to the hemispherectomy?

Few studies to date have examined post-operative sensorimotor impairments in hemispherectomised patients on the side ipsilateral to the surgery. Cairns & Davidson (1951) reported a slight tremor or general muscle weakness in the ipsilateral upper limb of a small number of their patients; however a subsequent study reported little, if any, change in ipsilateral functioning apart from the occasional increase in the reflexes (Obrador, 1964). More recent studies have shown ipsilateral motor impairments in hemiplegic patients (Brown et al. 1987, 1989; Colebatch & Gandevia, 1989; Jones et al. 1989). One study investigating ipsilateral somatosensory deficits in patients with unilateral brain damage suggested that the size of the excision or lesion was of particular importance in determining the extent of ipsilateral sensory deficits; the larger the excision the greater the ipsilateral sensory deficit (Corkin et al. 1970). If this hypothesis were to be true, it must indicate that patients following hemispherectomy will present with at least some ipsilateral sensory impairments. Indeed, in a study of somatosensory function in patients with unilateral lesions, the one patient with hemispherectomy showed ipsilateral deficits in graphesthesia (Knecht et al. 1996). However, all other tests of sensory function (for example two point discrimination, joint position sense, stereognosis and vibration perception) were reported as normal. More recently, an extensive study was carried out by Dijkerman (1996). He reported sensory and motor functional outcome in a group of 12 hemispherectomised paediatric patients. No deficits of the non-impaired ipsilateral limb were observed in basic motor functioning (such as peg sorting, force production, fine finger movement); the only deficit noted was in the ability to learn and subsequently perform manual sequences. In the same study,

somatosensory deficits were reported in the ipsilateral limb in tests of double simultaneous stimulation and pressure sensitivity. In keeping with these studies in humans, ipsilateral somatosensory deficits have also been seen in monkeys following unilateral excision of the sensorimotor region (Semmes & Mishkin, 1965).

7.1.4 Ipsilateral pathways in functional reorganisation in hemispherectomised patients

The studies reviewed above demonstrating varying degrees of residual motor function over different body parts are in keeping with reports that distal limb control is predominantly contralateral in cortical origin, with connections made via the corticospinal tract and rubrospinal brainstem pathway (passing from the red nucleus to the spinal cord). Proximal limb and axial body muscles and movements, however, are controlled bilaterally in the brain through the ventromedial brainstem system and ventrolateral tracts (see Section 1.3.4.1 of Chapter 1). Several studies put forward the hypothesis that the ability of the patient to use the distal portions of the limb (particularly the hand) contralateral to the hemispherectomised side was possible by the use of ipsilateral connections from the remaining hemisphere (for review see Glees & Cole, 1952; Zulch, 1974; Ameli, 1980; Muller et al. 1991). The origin of these ipsilateral connections remains unclear (refer to Section 1.5 of Chapter 1), and the various theories are discussed in detail below.

A small number of studies to date have demonstrated changes in the contralateral sensorimotor cortex following unilateral lesions of the other hemisphere (Jones & Schallert, 1989, 1992). This was revealed as an increase in the number of synapses per neurones and the volume and membrane surface area of dendritic processes per neurones (Jones et al. 1996). Studies of hemispherectomised animals have provided evidence that the motor cortex of the intact hemisphere shows significant thickening and an increase in dendritic arborization of pyramidal cells after early hemispherectomy (Kolb et al. 1983, 1992). Both studies highlight the potential for the cortex contralateral to the damaged side to undergo anatomical reorganisation.

The following sections review the work of previous SEP and fMRI studies on the identification and location of ipsilateral pathways in hemispherectomised patients.

7.1.4.1 Somatosensory evoked potential (SEP) studies

A number of studies using SEP recordings have been carried out to investigate the cortical structures involved in mediating the residual somatosensory functioning following hemispherectomy. The results of these studies however have been varied, and most were performed over a decade ago with little recent interest. Some studies have reported ipsilateral responses after stimulation of the median nerve contralateral to the removed hemisphere (Hazemann et al. 1969; Matsumita et al. 1971; Zulch & Micheler, 1978; Mauguiere & Desmedt, 1989). In these studies the ipsilateral cortical responses tended to consist only of long latency components compared to long and short components in the equivalent contralateral response (with the exception of short latency intact brainstem responses reported in Mauguiere & Desmedt, 1989). Villanueva & Castilla (1988) reported long latency and small amplitude ipsilateral responses in 2 of their 6 hemispherectomy cases. Such ipsilateral responses exist independently of any contralateral potentials, since in these patients one hemisphere has been functionally disconnected. Hazemann et al. (1969) hypothesised that the origin of the ipsilateral response may be through the extralemniscal sensory system. Several other studies in hemispherectomised patients did not show ipsilateral cortical responses in the intact hemisphere (Stohr & Goldring, 1969; Noel & Desmedt, 1980; Dijkerman et al. 1993). Studies failing to demonstrate ipsilateral SEP responses but in which the patient exhibits residual somatosensory function suggest that processing in a very small area of the cortex or possibly at a subcortical level (for example at the thalamus) may be sufficient for consciously perceiving a degree of sensation (Fukushima et al. 1976).

7.1.4.2 fMRI studies

To date, there have been few fMRI studies reported in hemispherectomised patients, and these mainly report case studies of one or two patients. Spencer et al. (1998) investigated active and passive movements of the normal and paretic hand in a single patient who underwent hemispherectomy at the age of 16 years. The patient had Rasmussen's encephalitis, with refractory seizures from the age of 12 years. They did not detect any activation following passive movement of the paretic hand, and cerebral activation associated with active and passive movement of the normal side was apparently more diffuse than expected, involving the premotor, supplementary motor and parietal areas. Using elbow flexion/extension (motor task) or tactile stimulation (sensory task), Graveline et al. (1998) investigated two patients who had undergone

hemispherectomy surgery at 9 years and 17 years of age. Both patients had had intractable seizures from less than 9 years of age; one had Sturge-Weber syndrome and the other had suffered a middle cerebral artery infarction. With the motor task, the patient who underwent surgery at age nine (patient 1) showed contralesional activation in the supplementary motor and premotor areas on movement of both hemiparetic and non-hemiparetic limbs, while the second patient showed only premotor cortex activation. In both cases, the premotor and supplementary motor area activations on movement of the hemiparetic limb were smaller in extent than those involving the normal limb. Sensory stimulation of the non-hemiparetic hand produced contralateral activations in the primary sensory and motor cortices, in the premotor and supplementary motor areas (patient 1 only), and in a region posterior to the somatosensory cortex. In patient 1, sensory stimulation of the hemiparetic hand was reported to activate similar areas to those activated with the non-hemiparetic hand, while the second patient only showed activation in the posterior somatosensory area. The authors suggest that the associative motor and sensory areas in the contralesional hemisphere may be sufficient to provide both sensation and movement in the hemiparetic limb following hemispherectomy.

7.1.5 Factors affecting functional outcome after hemispherectomy

As reviewed in Section 1.5 of Chapter 1, several factors may influence the functional outcome in a patient following unilateral brain injury or unilateral surgery such as hemispherectomy. Unilateral cerebral lesions that occur perinatally or in early childhood are reported by many researchers to be the most likely to be associated with good function post-operatively (among others, Benecke et al. 1991; Chugani et al. 1996). Muller et al. (1991) noted that the potential capability of the hemisphere to control ipsilateral distal movements is used fully when some damage to the motor system of the other hemisphere early in life causes a functional shift. Several groups have suggested other factors which may account for the less severe impairments observed in individuals who have undergone hemispherectomy. One additional factor is the greater the time period for functional recovery (or alternatively, the duration of intractable epilepsy) the better the residual function as more time has elapsed for cortical reorganisation to occur (St.James-Roberts, 1979, 1981; Vargha-Khadem et al. 1994). In contrast, if surgery is performed at an early age, this may enhance sensory and motor function post-operatively (Beckung et al. 1994). This may be due to the removal of the detrimental effects of seizures following successful surgery. It has also been suggested, however, that the age of the child at the time of the operation is less important in determining functional outcome, as sensorimotor function tends to only recover to the pre-operative capacity in

most cases (Gardner et al. 1955; Vargha-Khadem et al. 1997). This re-establishment occurs too early after the hemispherectomy to allow for other slower processes such as synaptic sprouting to provide additional reorganisation of function. Finally, prior to hemispherectomy, lesion size and location of the initial cortical damage has been shown to be a factor in determining functional outcome (for review see Chugani et al. 1996).

7.2 Methods

7.2.1 Patients

Patients were selected for the study if they had undergone either functional or anatomical hemispherectomy and were at least one year post-surgery. Only patients who were older than five years and were sufficiently co-operative to undergo SEP recordings were included in the study. As with the control subjects described in Chapter 6, all patients underwent investigations carried out on both hands ('normal' and 'hemiplegic' hand) for comparison.

7.2.2 Behavioural measures

Measures of sensory and motor function of the hands were obtained for all patients, as described in Chapter 5.

In order to visualise the behavioural data more easily, an average value was calculated from the patients' performance on the peg sorting, force production (dynamometer), and finger tapping tests, and the results of the residual motor function in the affected hand was given a graded score. The test results for force production and finger tapping for the affected hand were expressed as a percentage of the score achieved with the unaffected hand. In the case of the peg sorting test, the value used was the time taken using the unaffected hand as a percentage of the time required using the affected hand. A mean performance of greater than or equal to 80% was designated as normal function (****), 60%-79% was designated as mild deficit (***), 30%-59% was designated as moderate deficit (**), detectable function up to 30% was designated as severe deficit (*), and 0% was designated as no detectable function (0).

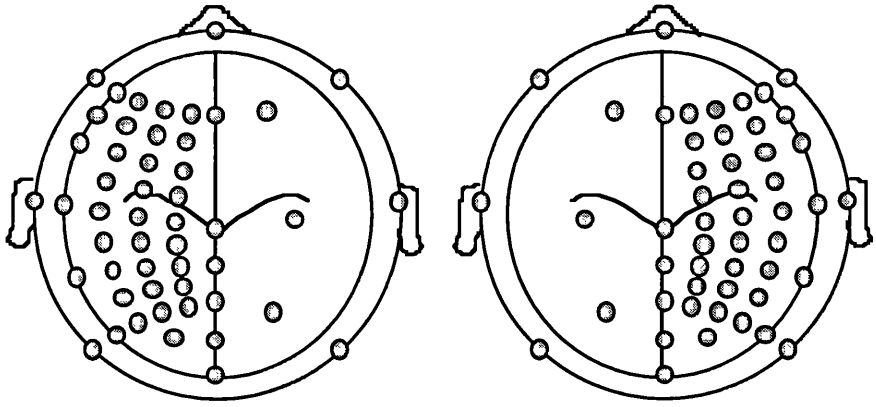
Similarly, for visualisation purposes, the patients' residual sensory function in the affected hand was graded according to their performance on the test of double

simultaneous stimulation (the test of joint position sense was performed in only 12 of 17 patients, and therefore could not be used in the classification of patients' sensory function). A score of greater than or equal to 80% correct responses was designated as normal function (****), scores between 60%-79% were designated as mild deficit (***), 30%-59% correct were designated as moderate deficit (**), 1%-29% correct were designated as severe deficit (*) and 0% was designated as no detectable function (0).

7.2.3 SEP recordings

The method and stimuli details used to record electrical and vibrational SEPs are described in Section 4.2 of Chapter 4. All of the patients underwent SEP investigations to electrical stimuli applied above motor threshold (M+S intensity). In an attempt to corroborate the findings from electrical stimulation, ten of the more co-operative patients also underwent SEP recordings in response to vibration stimuli. Vibration stimuli were delivered to the index and middle finger tips (median nerve stimulation).

Recordings were taken from a total of 50 electrodes, with the majority of electrodes located over the intact hemisphere. Since the location of any ipsilateral response could not be assumed in advance, a large number of electrodes were used to ensure the response could be detected, particularly if it proved to have a field of small spatial extent. Schematic representations of the montages used for the SEP recordings in left and right hemispherectomy cases are depicted in Figure 7.1. A small number of electrodes were also placed over the hemispherectomised side to balance the recording positions over the whole of the brain for post-processing mapping (2-dimensional topographical voltage maps). All averages were referenced to two frontal electrodes over the side of the excision. Recordings were made following separate stimulation of both the normal and hemiplegic hand. In every case, ipsilateral potentials could be directly compared to normal contralateral responses, as data were acquired in the same session. The largest early latency (10-200 ms) ipsilateral positive or negative component was used for analysis and display. Amplitude measurements from the waveforms were taken from the first peak to peak distance of different polarities and the latency was measured from the earliest positive or negative components (see Section 4.2.2 of Chapter 4). Paired t-tests were performed between contralateral and ipsilateral measurements.



right hemispherectomy left hemispherectomy

Figure 7.1: Montages used in patients with left and right hemispherectomies.

7.2.4 Functional MRI

Patients were excluded from fMRI investigations if they had potentially magnetic vascular clips within the brain, or were too young or intellectually impaired to achieve the required level of co-operation.

A number of hand sensorimotor tasks were performed with fMRI, depending on the level of co-operation of the patients. All patients underwent passive movement of both the normal and hemiplegic hand. Many patients were unable to move the hand contralateral to the side of surgery, and often the hand was spastic and difficult to move. Therefore, in contrast to the method of passive movement using a restraint in the control subjects (Chapter 6), passive movement was performed by the examiner moving the patients' fingers in and out of the palm with a flexion/extension movement of the metacarpophalageal joints. While the patient lay in the scanner, the elbow was supported with light padding on both sides for comfort and to raise the hand slightly to assist the examiner to reach the hand. Passive movement was performed at a rate of approximately 2 Hz. A total of 120 images were collected, divided into 12 task/rest cycles with 5 data sets in each state. The collected images were realigned and analysed using SPM, as described in Section 3.2.1 of Chapter 3. Activation maps were spatially smoothed to three times the original voxel size. P-values are reported as uncorrected or corrected for multiple comparisons.

Active movement was also performed with the ipsilesional hand using the same paradigm as above. This was to establish the location of fMRI activation using a more sensitive task. The patient was instructed to move the fingers of the hand towards and

away from the palm, extending the fingers fully in-between, at a rate of approximately 2 Hz (comparable with the passive movement task).

Finally, in three of the more co-operative patients who agreed to further testing, electrical stimulation (at 4 Hz) of the contralesional hand was performed using an identical method to that described in Section 6.2.2.3 of Chapter 6 for the controls subjects and the acquisition paradigm outlined above.

As many of the above experiments as possible were performed within the same session to allow a direct comparison between results. In particular, it was aimed to carry out passive movement of both hands in the same session. In most cases, active movement and electrical stimulation experiments were carried out in separate sessions.

7.2.5 Statistical Analysis

Statistical analyses were carried out on the fMRI and SEP data in relation to the behavioural test results (using the raw data for each of the tests), age at injury, age at surgery, duration of epilepsy, and side of hemispherectomy. The results obtained from the statistical analyses are included for completeness, recognising that these lack power due to the small sample size used in this study. For the behavioural test results, ipsilesional observations were used as an index of inherent performance. Given that the range of values obtained from the ipsilesional observations was generally small compared with the range of contralesional values, the ratio of the two observations was used as a response variable, thus providing a simple adjustment for inherent performance. Examination of the response data showed three different categories of distribution behaviour. Accordingly, one of the following statistical analyses were performed as appropriate.

Category 1: In those cases in which the observed value of the dependant variable is mostly zero with some non-zero values then a binary response variable (zero or non-zero) was generated, forming a 2x2 contingency table. Given the small frequencies involved, Fisher's Exact test was used.

Category 2: Those not belonging to category 1, but in which the identical distribution assumption could not be invoked, the Wilcoxon-Mann-Whitney test was used as a test of association (as opposed to its usual use as a test of the equality of 2 medians).

Category 3: Those cases not belonging to categories 1 and 2 were examined using a general linear model analysis (regression analysis). An interaction term was included in the model to test for disease group differences (congenital versus acquired), recognising that this test lacks power. In no event was the interaction term significant and, accordingly, the main effect *p*-values are quoted.

7.3 Results

7.3.1 Summary of patient population

Seventeen patients were involved in this study, with ages ranging from 6 to 19 years (mean 14 years 1 month). There were 7 females and 10 males. Details of the 17 patients involved in the study are shown in Table 7.1. Patients were divided into two groups; those with congenital disease (8 patients) and those with acquired disease (9 patients). Table 7.2 summarises the data of the two groups (patients 1 to 8 have congenital disease and patients 9 to 17 have acquired disease). There was a difference between the mean age at first seizure between these two groups (1 year 7 months in patients with congenital disease, compared to 4 years 4 months in patients with acquired disease). The mean age at surgery (10 years 3 months and 9 years 6 months for patients with congenital and acquired disease, respectively) and the mean age at the time of investigation (15 years 3 months and 13 years 1 month for patients with congenital and acquired disease, respectively) were similar for the two groups.

Patient	Age at first seizure (yrs.mths)	Etiology/ pathology	Age at surgery (yrs.mths)	Side/type of operation	Age at time of investigation (yrs.mths)
1 (PO)	0.0	Sturge Weber syndrome	8.7	left/func	17.0
2 (AB)	0.0	middle cerebral artery infarct	9.8	left/anat	15.0
3 (PP)	0.0	hemimegelencephaly	0.4	right/anat	6.8
4 (FC)	0.1	cortical dysplasia	15.4	left/func	19.0
5 (CB)	0.7	intractable seizures/gliosis	12.4	left/func	14.2
6 (EBa)	1.6	extradural cyst	13.9	left/func	18.2
7 (TDR)	4.5	porencephaly	11.10	right/func	13.1
8 (HW)	7.0	cortical dysplasia	10.5	left/anat	19.5
9 (PG)	1.7	encephalitis	5.2	left/func	9.0
10 (TB)	2.4	Rasmussen's encephalitis	11.8	right/func	12.6
11 (RG)	2.5	middle cerebral artery infarct	9.6	left/func	13.7
12 (PD)	3.7	Rasmussen's encephalitis	4.1	left/func	9.0
13 (MS)	4.4	Rasmussen's encephalitis	7.0	right/func	14.0
14 (BCS)	4.8	Rasmussen's encephalitis	6.10	left/func	8.7
15 (KD)	6.0	Rasmussen's encephalitis	11.9	right/anat	16.0
16 (ML)	7.0	middle cerebral artery infarct	14.9	right/func	18.0
17 (EBr)	8.0	Rasmussen's encephalitis	15.10	right/func	17.0

Table 7.1: Patient details (func=functional hemispherectomy, anat=anatomical hemispherectomy). Patients 1 to 8 have congenital disease, patients 9 to 17 have acquired disease.

	Congenital	Acquired
Number of patients	8	9
Mean age of first seizure	1 year 7 months (0-7)	4 years 4 months (1.7-8)
Mean duration of epilepsy pre-operatively	8 years 6 months (0.4-15.3)	5 years 2 months (0.6-9.3)
Mean age at surgery	10 years 3 months (0.4-15.4)	9 years 6 months (4.1-15.10)
Side of surgery	6 x left 2 x right	4 x left 5 x right
Mean age at time of investigations	15 years 3 months (6.8-19.5)	13 years 1 month (8.7-18)

Table 7.2: Summary of patient details shown in Table 7.1. (Age range in years.months shown in brackets).

7.3.2 Behavioural results

The behavioural results for the individual patients are shown in Table 7.3 (motor function) and Table 7.4 (sensory function).

Patient	Side of damage	Age at testing (yrs.mths)	Tapping	Dynamometer	Peg sorting	Mirror movements?	Summary of residual function
1 (PO)	left	17.0	i/l=116 c/l=14	i/l=38 c/l=2	i/l=16 c/l=120	N	*
2 (AB)	left	15.0	i/l=91 c/l=0	i/l=22 c/l=0	i/l=13 c/l=-	N	0
3 (PP)	right	6.8	i/l=59 c/l=0	i/l=11 c/l=0	i/l=18 c/l=-	N	0
4 (FC)	left	19.0	i/l=79 c/l=0	i/l=26 c/l=0	i/l=10 c/l=-	N	0
5 (CB)	left	14.2	i/l=53 c/l=0	i/l=11 c/l=0	i/l=13 c/l=-	N	0
6 (EBa)	left	18.2	i/l=73 c/l=57	i/l=24 c/l=5	i/l=10 c/l=38	Y	**
7 (TDR)	right	13.1	i/l=53 c/l=0	i/l=20 c/l=1	i/l=25 c/l=-	Y	*
8 (HW)	left	19.5	i/l=102 c/l=54	i/l=26 c/l=11	i/l=9 c/l=35	Y	**
9 (PG)	left	9.0	i/l=65 c/l=0	i/l=10 c/l=0	i/l=19 c/l=-	N	0
10 (TB)	right	12.6	i/l=50 c/l=0	i/l=23 c/l=0	i/l=15 c/l=-	N	0
11 (RG)	left	13.7	i/l=86 c/l=0	i/l=25 c/l=0	i/l=10 c/l=-	N	0
12 (PD)	left	9.0	i/l=73 c/l=0	i/l=20 c/l=0	i/l=10 c/l=-	N	0
13 (MS)	right	14.0	i/l=105 c/l=0	i/l=31 c/l=0	i/l=11 c/l=-	N	0
14 (BCS)	left	8.7	i/l=60 c/l=0	i/l=18 c/l=0	i/l=14 c/l=-	N	0
15 (KD)	right	16.0	i/l=96 c/l=0	i/l=22 c/l=0	i/l=10 c/l=-	N	0
16 (ML)	right	18.0	i/l=119 c/l=0	i/l=23 c/l=0	i/l=10 c/l=-	N	0
17 (EBr)	right	17.0	i/l=106 c/l=0	i/l=32 c/l=0	i/l=9 c/l=-	N	0

Table 7.3: Motor tests in patients with congenital (patients 1 to 8) and acquired (patients 1 to 9) disease. Units/abbreviations are as follows; tapping=number per 20 seconds, dynamometer=kg, Peg sorting=seconds, i/l=ipsilateral to surgery, c/l=contralateral to surgery. * and ** indicate degree of residual contralateral motor function (see methods Section 7.2.2). - indicates those patients who were unable to complete the task. Data from patients who show a degree of residual motor function are shaded red.

Patient	Side of damage	Age at testing (yrs.mths)	Double sim.stim. -hand	Position sense	Summary of residual function
1 (PO)	left	17.0	i/l=100 c/l=28	i/l=100 c/l=0	*
2 (AB)	left	15.0	i/l=94 c/l=33	x	**
3 (PP)	right	6.8	i/l=94 c/l=11	x	*
4 (FC)	left	19.0	i/l=89 c/l=33	i/l=100 c/l=60	**
5 (CB)	left	14.2	i/l=94 c/l=33	i/l=93 c/l=0	**
6 (EBa)	left	18.2	i/l=100 c/l=11	i/l=100 c/l=0	*
7 (TDR)	right	13.1	i/l=100 c/l=17	x	*
8 (HW)	left	19.5	i/l=100 c/l=78	i/l=100 c/l=0	***
9 (PG)	left	9.0	i/l=94 c/l=0	x	0
10 (TB)	right	12.6	i/l=94 c/l=17	i/l=82 c/l=0	*
11 (RG)	left	13.7	i/l=100 c/l=67	i/l=98 c/l=0	***
12 (PD)	left	9.0	i/l=100 c/l=0	i/l=100 c/l=0	0
13 (MS)	right	14.0	i/l=100 c/l=17	i/l=100 c/l=0	*
14 (BCS)	left	8.7	i/l=100 c/l=0	x	0
15 (KD)	right	16.0	i/l=100 c/l=11	i/l=100 c/l=0	*
16 (ML)	right	18.0	i/l=100 c/l=33	i/l=100 c/l=0	**
17 (EBr)	right	17.0	i/l=94 c/l=50	i/l=100 c/l=0	**

Table 7.4: Sensory tests. Test results show percent of responses correct. (Double sim.stim.-hand=double simultaneous stimulation to the hand, i/l=ipsilateral to surgery, c/l=contralateral to surgery. *-*** indicate degree of residual contralateral sensory function (see methods Section 7.2.2). Tests that were not performed in any individual patient are denoted x. Patients who show a degree of residual sensory function are shaded red.

All 8 patients with congenital disease had some residual sensory function in the hand contralateral to the hemispherectomised side on double simultaneous stimulation. Four of the patients had a severe sensory deficit, three had a moderate sensory deficit and one had only a mild sensory deficit. None of the patients had normal sensory function. Four of the patients with congenital disease also showed residual motor function on dynamometer. Three of these patients also showed residual function on tapping and peg sorting. Two patients had a severe motor deficit and two had a moderate deficit. Of these four patients, three had mirror movements (patients 6, 7, and 8), and one patient had independent hand movements (patient 1).

Of the 9 patients with acquired disease, 6 showed residual sensory function, including patients with early onset and with late onset of epilepsy. Three patients had a severe sensory deficit, two had a moderate deficit and only one had a mild sensory deficit. None of the patients had normal sensory function in the affected hand, compared to the

unaffected hand. In addition, none of these patients demonstrated any residual motor function in the hand contralateral to the surgically removed hemisphere.

Patients with congenital disease appeared to be more likely to show residual sensory and motor function. Within the acquired group, there appears to be no relationship between the age at first seizure and sensorimotor function, i.e. patients who had both early and late onset of epilepsy showed residual sensory function (compare Table 7.3 and Table 7.4 with Table 7.1).

7.3.3 SEP results

All 17 patients demonstrated clear and reproducible contralateral electrical and vibrational SEPs on stimulation of the normal side, which were similar in appearance and location to those recorded in adult and child controls (see Sections 6.3.1.2 and 6.3.2.3 of Chapter 6). The results for all patients are presented in a similar layout. Each figure contains a schematic representation of the montage which was used for the patient (depending on the side of surgery). Selected waveforms of the peak activity location for stimulation of the normal (contralateral SEP) and hemiplegic (ipsilateral SEP) side are shown on the right of the figure (the waveforms of selected electrodes displayed are indicated on the montage by the following colour coding: blue corresponds to peak contralateral SEP, red corresponds to peak ipsilateral SEP, and green is used if the electrode shows the peak activity for both ipsilateral and contralateral SEP responses). Finally 2-D topographical voltage maps for specific time points from stimulation of each side (each headed normal and hemiplegic for stimulation of each side) are presented in the bottom left portion of the figure. The earliest clearly recognisable and reproducible positive or negative cortical components for contralateral and ipsilateral SEPs are compared and analysed in the 2-D voltage maps. With the exception of one case (patient 15), an early component in the ipsilateral response could be clearly identified and compared to a similar early contralateral response of the same polarity. For patient 15, early response components following electrical and vibrational stimuli of different polarity were compared. The locations of ipsilateral potentials can be directly compared to normal contralateral responses as data were acquired in the same session. Due to the poor spatial resolution of this technique, however, only large shifts in the peak locations of the responses are identifiable (peak locations for each of the responses are indicated on the montages in each of the figures showing patient results). Below are the results of patients who demonstrated an ipsilateral response with stimulation of the hemiplegic

hand. Note that the amplitude and latency scales for the waveforms and the scales for the voltage maps may differ between figures.

7.3.3.1 Electrical SEPs

7.3.3.1.1 Patients with Congenital Disease

Five out of eight patients with congenital disease demonstrated ipsilateral SEPs on electrical stimulation of the hemiplegic side. The remaining three patients did not show an ipsilateral response on electrical stimulation of the hemiplegic hand. The results for the five patients are shown below (Figure 7.2 to Figure 7.6).

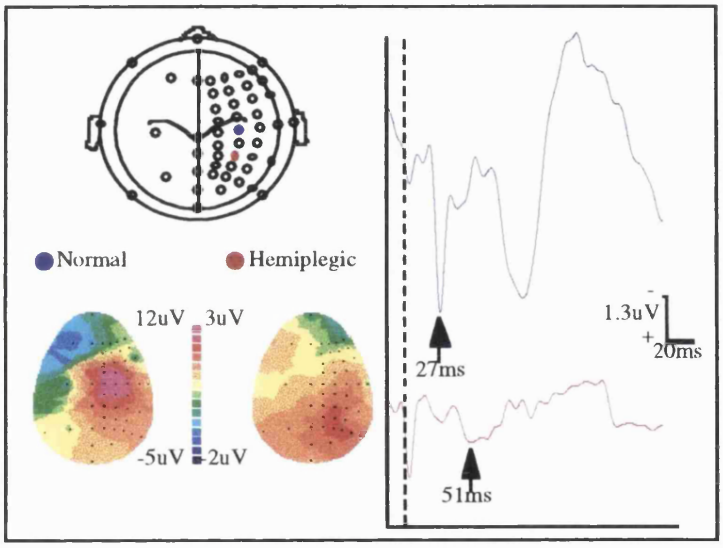


Figure 7.2: Patient 1. Electrical SEPs - see Section 7.3.3 for description of conventions

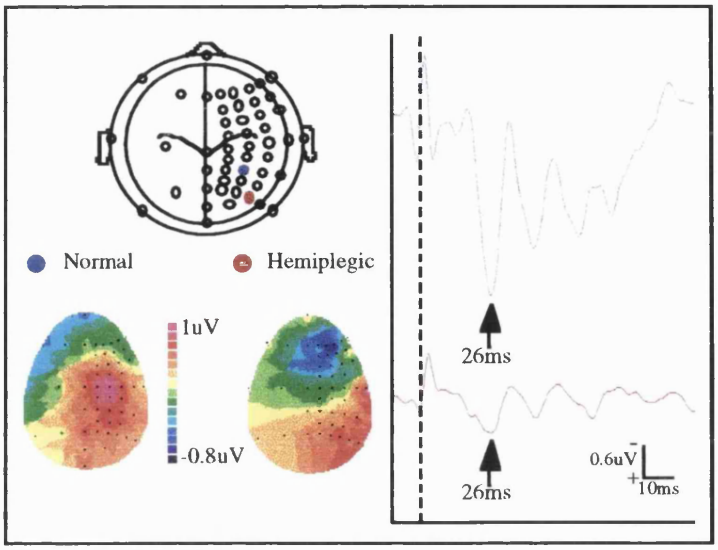


Figure 7.3: Patient 4. Electrical SEPs - see Section 7.3.3 for description of conventions

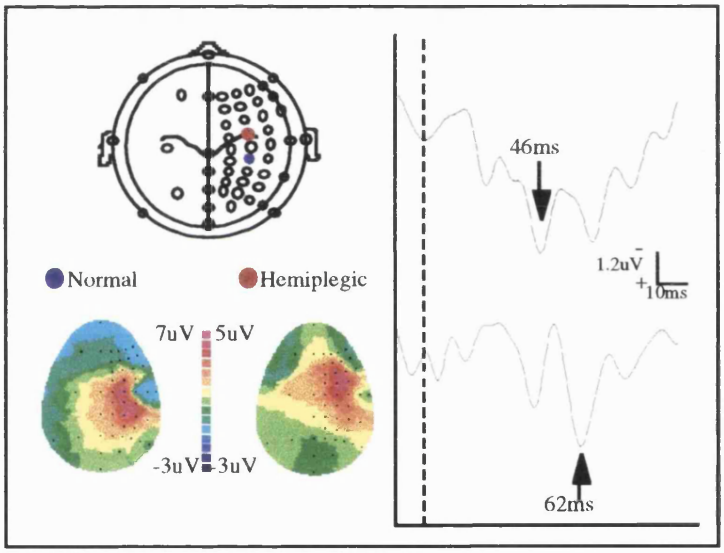


Figure 7.4: Patient 5. Electrical SEPs - see Section 7.3.3 for description of conventions

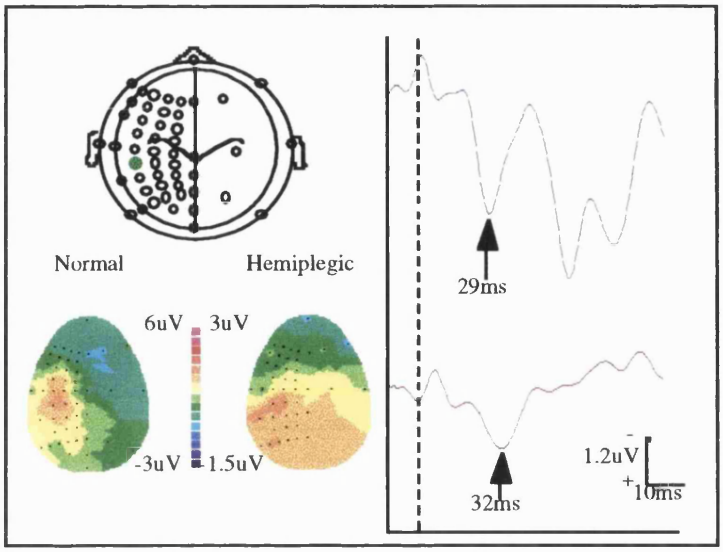


Figure 7.5: Patient 7. Electrical SEPs - see Section 7.3.3 for description of conventions

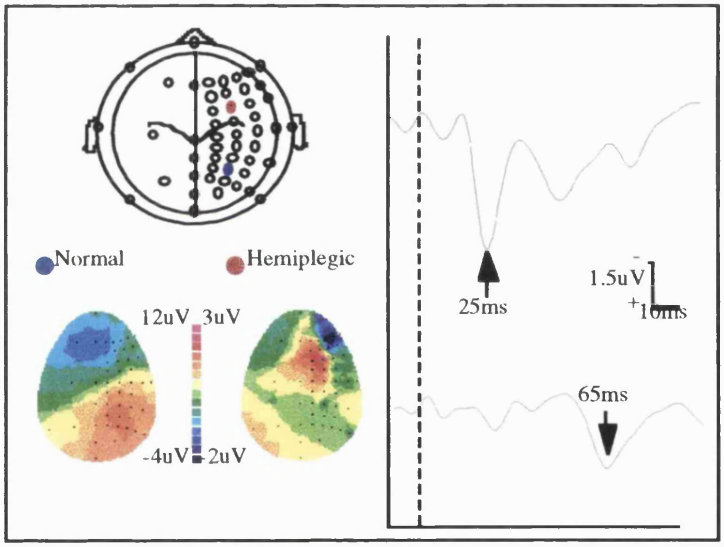


Figure 7.6: Patient 8. Electrical SEPs - see Section 7.3.3 for description of conventions

7.3.3.1.2 Patients with Acquired Disease

Of the nine patients with acquired disease, 5 patients demonstrated ipsilateral electrical SEPs following stimulation of the hemiplegic hand. The remaining four patients did not show an ipsilateral response following electrical stimulation of the hemiplegic hand. The results of the five patients are presented below (Figure 7.7 to Figure 7.11).

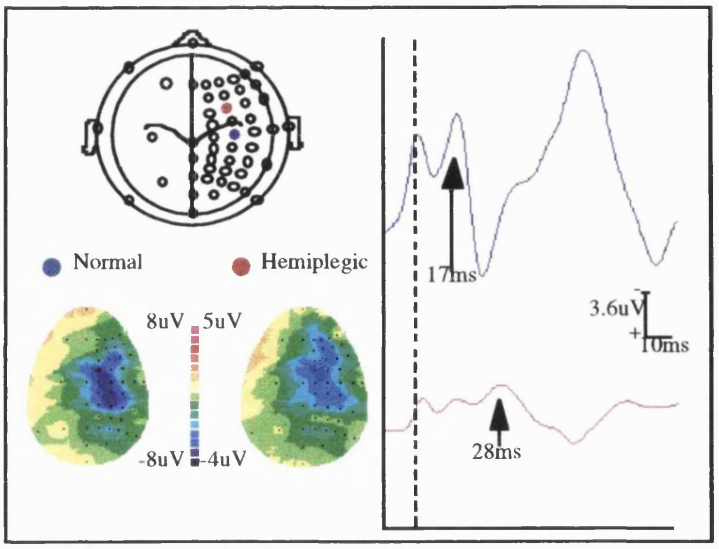


Figure 7.7: Patient 9. Electrical SEPs - see Section 7.3.3 for description of conventions

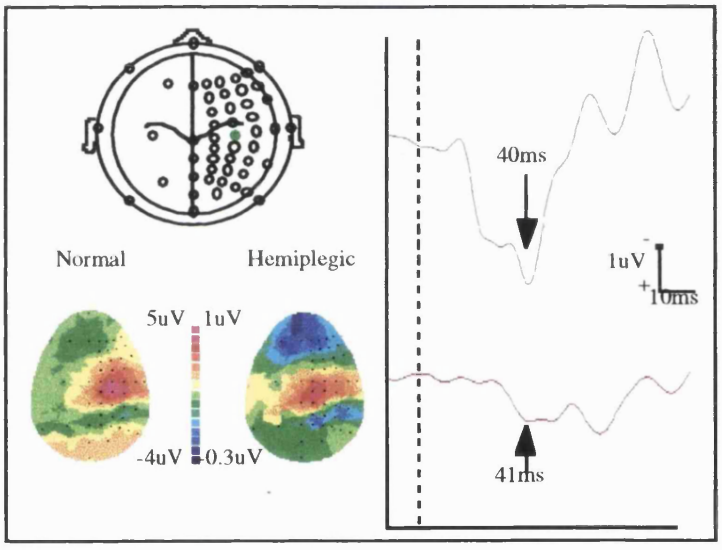


Figure 7.8: Patient 11. Electrical SEPs - see Section 7.3.3 for description of conventions

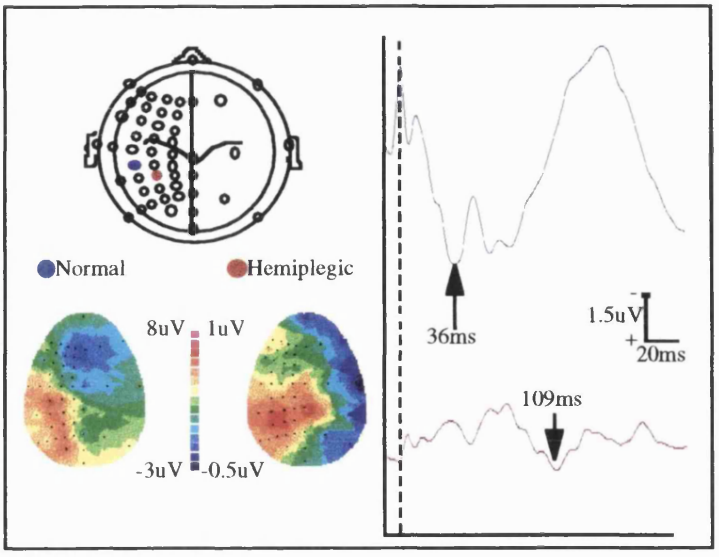


Figure 7.9: Patient 13. Electrical SEPs - see Section 7.3.3 for description of conventions

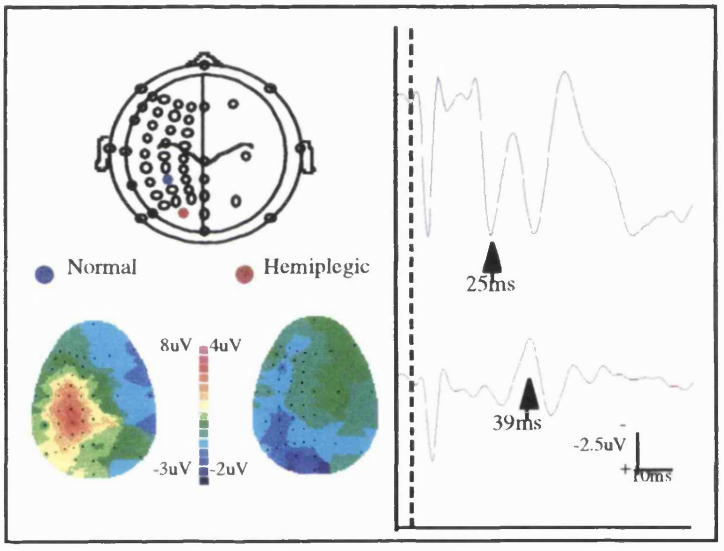


Figure 7.10: Patient 15. Electrical SEPs - see Section 7.3.3 for description of conventions

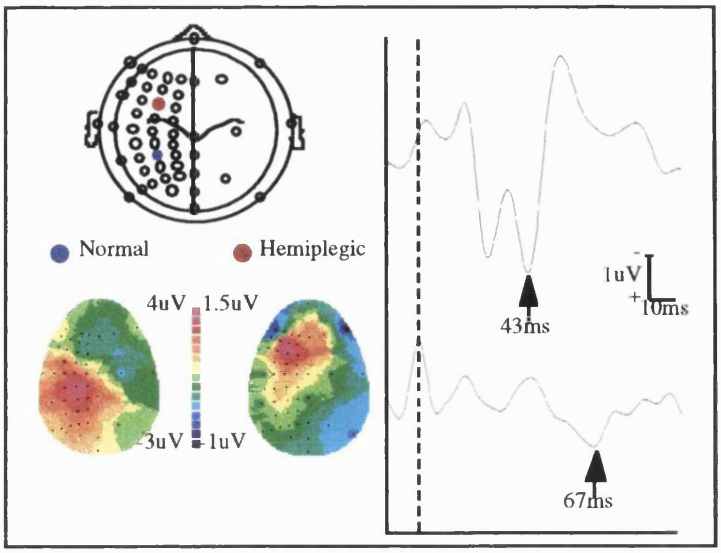


Figure 7.11: Patient 16. Electrical SEPs - see Section 7.3.3 for description of conventions

7.3.3.1.3 Summary of SEP responses following electrical stimulation

In summary, 10 of the 17 patients demonstrated ipsilateral SEP responses following electrical stimulation of the hemiplegic hand (5 with congenital and 5 with acquired disease). Of those patients who demonstrated ipsilateral SEPs, the latency of the earliest and most clearly defined positive or negative component was significantly longer ($P<0.005$; paired t-test) for responses from the hemiplegic side than for responses from stimulation of the normal side (mean±standard deviation = 30.4±8.8 ms compared to 45.6±15.2 ms for stimulation of the normal and hemiplegic sides, respectively). In addition, the amplitude of the earliest peak to peak component was significantly smaller ($P<0.0005$; paired t-test) for responses to stimulation of the hemiplegic side than for stimulation of the normal side (mean±standard deviation 2.36±1.6μV compared to 6.46±2.7μV, respectively). The peak locations of the response to stimulation of the normal and hemiplegic side varied between patients. In seven out of the 10 patients who demonstrated ipsilateral responses following electrical stimuli, the peak location of the ipsilateral response was in a similar position (within one or two electrodes) to the peak response from stimulation of the normal (contralateral) side (patients 1,4,5,7,9,11,13). Two patients demonstrated a peak ipsilateral response that was more than 2 electrode positions (approximately 4-10 cm) anterior to the peak contralateral location (patients 8 and 16). Finally, one patient demonstrated peak ipsilateral responses that were more than 2 electrode positions (4-6 cm) posterior to the peak contralateral response (patient 15).

7.3.3.2 Vibrational SEPs

For all of the patients who underwent vibrational SEP investigations, normal contralateral responses were recorded following stimulation of the unaffected hand. Individual vibrational SEP components were longer in latency and smaller in amplitude compared to their electrical stimuli counterparts (also shown in Section 4.3 of Chapter 4).

7.3.3.2.1 Patients with Congenital Disease

SEPs following vibration stimuli were recorded in only 3 of the 8 patients with congenital disease. Of these three patients, two patients demonstrated ipsilateral SEPs on vibration stimuli of the hemiplegic side (Figure 7.12 and Figure 7.13). The other patient did not show an ipsilateral response on vibrational stimulation of the hemiplegic hand.

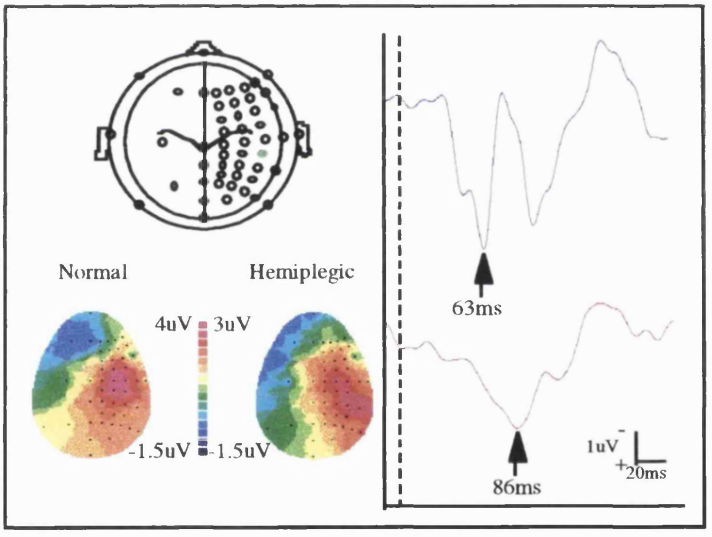


Figure 7.12: Patient 1. Vibrational SEPs - see Section 7.3.3 for description of conventions

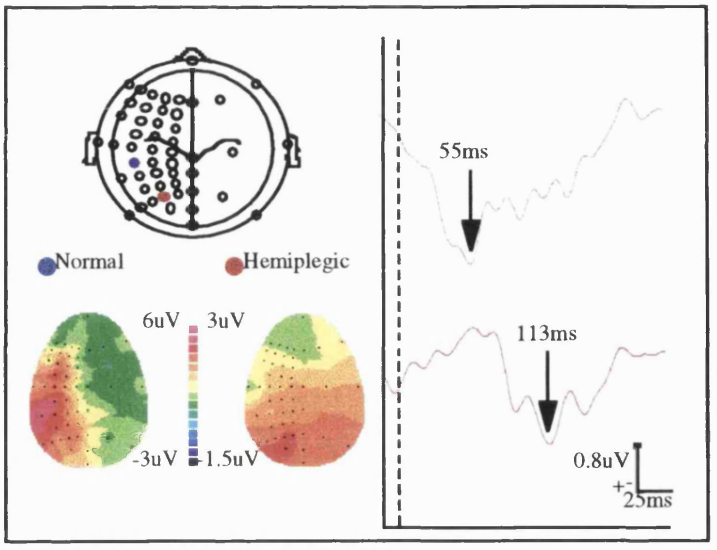


Figure 7.13: Patient 7. Vibrational SEPs - see Section 7.3.3 for description of conventions

7.3.3.2.2 Patients with Acquired Disease.

Seven of the nine patients with acquired disease underwent SEP recordings following vibration stimuli. Of these seven patients, three patients showed ipsilateral SEPs on vibration stimuli applied to the hemiplegic side (Figure 7.14 to Figure 7.16). The remaining four patients did not demonstrate an ipsilateral response with vibrational stimulation of the hemiplegic hand.

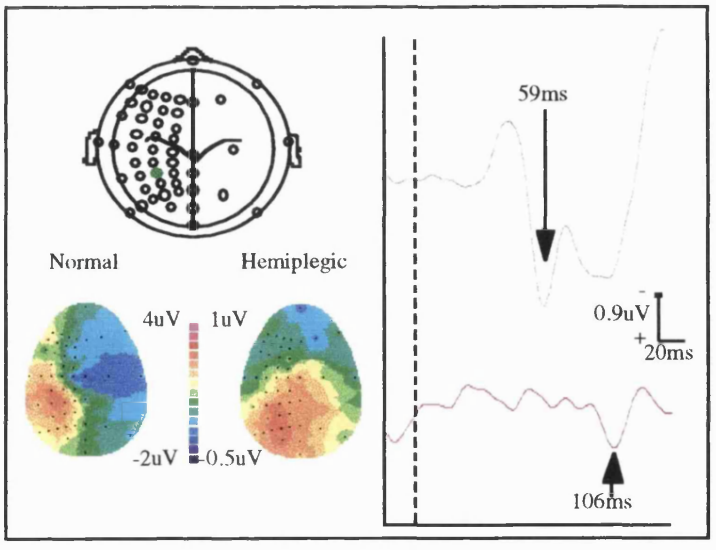


Figure 7.14: Patient 13. Vibrational SEPs - see Section 7.3.3 for description of conventions

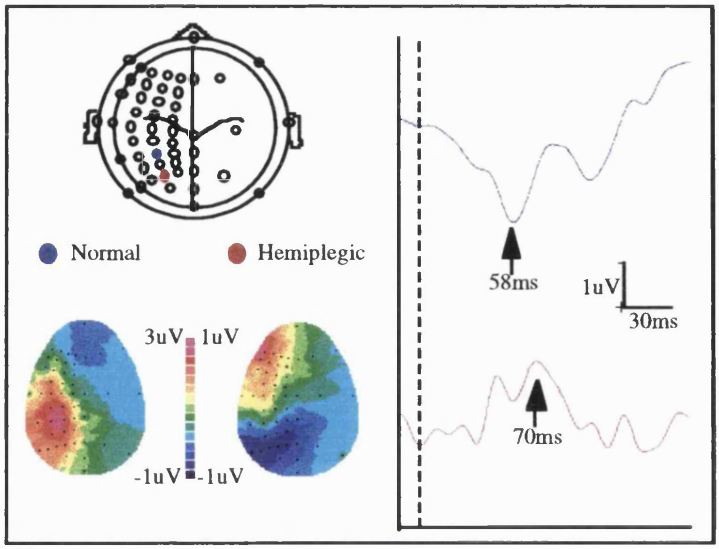


Figure 7.15: Patient 15. Vibrational SEPs - see Section 7.3.3 for description of conventions

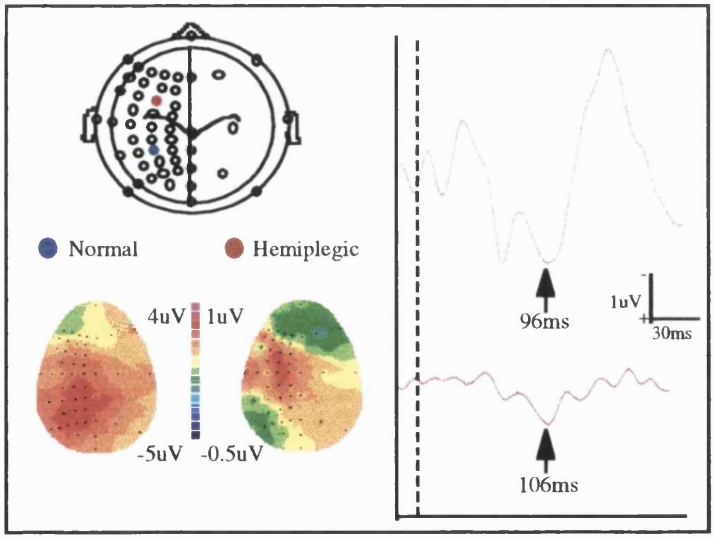


Figure 7.16: Patient 16. Vibrational SEPs - see Section 7.3.3 for description of conventions

7.3.3.2.3 Summary of SEP responses following vibrational stimulation

In summary, 5 out of 10 patients demonstrated ipsilateral SEPs on vibration stimuli (2 with congenital and 3 with acquired disease). Of those patients who demonstrated ipsilateral SEPs, the latency of the early components was significantly longer ($p<0.05$; paired t-test) for responses from the hemiplegic side compared to stimulation of the normal side (mean±standard deviation = 96.2±17.8 ms compared to 66.2±16.9 ms respectively). In addition, the amplitude of the early component was significantly

smaller ($p<0.01$; paired t-test) for responses following stimulation of the hemiplegic hand compared to the normal hand (mean±standard deviation 1.35±0.5μV compared to 3.72±0.8μV respectively). With vibrational stimulation, there was a slight different in the location of ipsilateral compared to contralateral responses. Patient 7 showed ipsilateral responses greater than 2 electrode positions anterior to the peak contralateral response, and patient 15 did not show a difference in the location of the peak responses with stimulation of either hand. Patients 1 and 13 had similar peak SEP locations from stimulation of the normal and hemiplegic side, and patient 16 showed an ipsilateral SEP response which was anterior to the peak response from stimulation of the normal side.

7.3.3.3 Summary of electrical and vibrational SEPs in patients with congenital and acquired disease.

In total, 10 patients from the total of 17 demonstrated ipsilateral SEP responses with electrical stimulation. Ten of the 17 patients also underwent SEP recordings following vibrational stimulation, with 5 demonstrating ipsilateral SEPs (for a summary of the results see Table 7.5). In all cases, ipsilateral vibrational SEPs following stimulation of the hemiplegic side were only present in patients who also demonstrated ipsilateral electrical SEPs. The location of the ipsilateral vibrational SEP response was similar to the equivalent ipsilateral electrical SEP response in each of the 5 cases. Patients with both congenital and acquired disease showed the presence of ipsilateral SEPs, and there appears to be no significant relationship between the demonstration of ipsilateral SEPs and the onset of neurological disease in this group of patients.

Patient - congenital	Ipsilateral electrical SEPs	Ipsilateral vibration SEPs
1 (PO)	Y	Y
2 (AB)	N	X
3 (PP)	N	X
4 (FC)	Y	X
5 (CB)	Y	X
6 (EBa)	N	X
7 (TDR)	Y	Y
8 (HW)	Y	N

Patient - acquired	Ipsilateral electrical SEPs	Ipsilateral vibration SEPs
9 (PG)	Y	X
10 (TB)	N	N
11 (RG)	Y	N
12 (PD)	N	N
13 (MS)	Y	Y
14 (BCS)	N	N
15 (KD)	Y	Y
16 (ML)	Y	Y
17 (EBr)	N	X

Table 7.5: Summary of results of SEP recordings in patients with congenital and acquired disease. Patients who demonstrated ipsilateral electrical SEPs are in green, those with ipsilateral electrical and vibrational SEPs in red, and patients who did not show ipsilateral SEPs with either stimuli in black. x indicates patients who did not carry out SEP investigation on vibration stimuli.

7.3.4 fMRI results

Eight of the 17 patients underwent fMRI. Of these eight patients, four patients had congenital disease (patients 1, 2, 4 and 6) and four had acquired disease (patients 12, 15, 16, 17) (refer to Table 7.1). A summary of the relevant details for the patients in each of these groups is shown in Table 7.6. As with the overall patient population (Table 7.2), there is a large difference in the mean age of first seizure between the two groups (4 months in patients with congenital disease, compared to 6 years 2 months in patients with acquired disease). However, the mean age at surgery (12 years and 11 years 5 months for patients with congenital and acquired disease, respectively) and the mean age at the time of investigation (17 years 3 months and 15 years for patients with congenital and acquired disease, respectively) were similar for the two groups.

	Congenital	Acquired
Number of patients	4	4
Mean age of first seizure	4 months (0-1.6)	6years 2months (3.7-8.0)
Mean duration of epilepsy pre-operatively	11.5 years (8.7-15.3)	5.4 years (0.6-7.9)
Mean age at surgery	12 years (8.7-15.4)	11years 5months (4.1-15.10)
Side of surgery	4 x left	1 x left 3 x right
Mean age at time of investigations	17years 3months (15-19)	15 years (9-18)

Table 7.6: Details of patient groups with congenital and acquired disease who underwent fMRI investigations. (Age range in years.months shown in brackets).

7.3.4.1 Active movement of the normal hand (ipsilateral to surgery)

Six of the eight patients who underwent fMRI (all except patients 4 and 16) performed active movement of the normal hand, ipsilateral to the hemispherectomised side. All six patients showed contralateral activation in the sensorimotor cortex in the remaining hemisphere which was similar in location and distribution to that from adult and child control subjects described in Sections 6.3.1.1 and 6.3.2.2 of Chapter 6.

7.3.4.2 Passive movement

All eight patients underwent fMRI studies of passive movement of the normal and hemiplegic hand. Normal contralateral sensorimotor cortex activation was observed on passive movement of the normal hand in each case. For each dataset, the threshold used for the display of activated regions is an uncorrected p-value. In addition, those regions which achieved a corrected level of significance are also described.

7.3.4.2.1 Patients with congenital disease

One of the four patients (patient 4) with congenital disease demonstrated ipsilateral sensorimotor cortex activation with passive movement of the hemiplegic hand (Figure 7.17). The other three patients did not show any activation in the sensorimotor areas with passive movement of the hemiplegic hand. The activation map obtained with passive movement of the hemiplegic hand was thresholded at a higher significance level than that with movement of the normal side to remove background noise due to head motion. The images are displayed at an uncorrected p-value threshold of $p<0.01$ for the normal hand and $p<0.0001$ for the hemiplegic hand (extent threshold $p<0.05$). Within each experiment the significance of activation can be compared, with yellow pixels being more significant than red; however the significance of activation cannot be directly compared between experiments (see Section 3.5 of Chapter 3). The ipsilateral activation observed with passive movement of the hemiplegic hand appears to be similar in location to contralateral sensorimotor cortical activation with passive movement of the normal hand and extends through at least four slices (each 3 mm thick), as seen in Figure 7.17. There also appears to be a region of activation situated slightly posterior to that activated with movement of the normal side, which could be due to the presence of proprioceptive cues that are intrinsic to any voluntary motor activity (Picard & Smith, 1992). Both of these regions also achieve corrected significance at $p<0.0001$. The peak activation extends deeper within the central sulcus for passive movement of the normal hand (a), but is located maximally at the edge of the brain, most likely in the region of superficial draining veins, for passive movement of the hemiplegic hand (b).

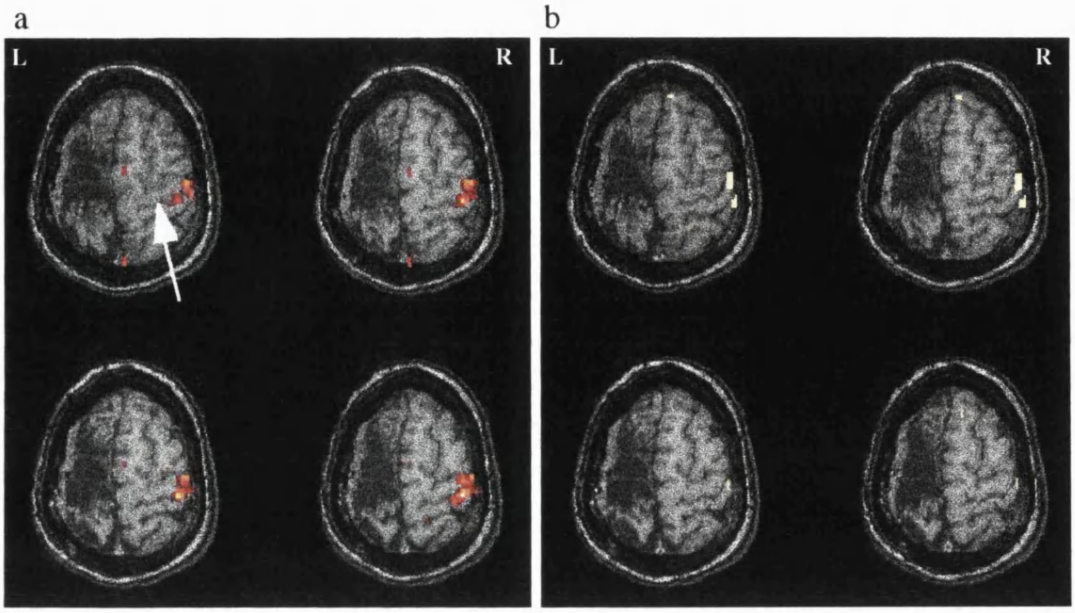


Figure 7.17: Patient 4: Four adjacent axial slices shown over the region of the sensorimotor cortex. Sensorimotor cortex activation (central sulcus indicated by arrow) on passive movement of the normal (left) hand, labelled a, and on passive movement of the hemiplegic (right) hand, labelled b. There is also activation of the SMA on passive movement of the normal hand located medially in the frontal lobe (a).

7.3.4.2.2 Patients with acquired disease

One of the four patients (patient 16) with acquired disease demonstrated ipsilateral sensorimotor cortex activation on passive movement of the hemiplegic hand (Figure 7.18b). The other three patients did not show any activation in the sensorimotor areas on passive movement of the hemiplegic hand. The same colour coding applies for the levels of significance within an experiment as in Section 7.3.4.2.1, with yellow showing pixels of greater significance than red. The images are displayed at an uncorrected threshold of $p<0.01$ (extent threshold $p<0.05$). The ipsilateral activation on passive movement of the hemiplegic hand appeared to be located in the anterior portion of the activated region seen with passive movement of the normal hand (comparison of a and b from Figure 7.18). The peak location of ipsilateral activation in these particular slices is along the precentral sulcus, immediately anterior to the primary motor cortex and consistent with activation of the premotor cortex. The activation on passive movement of the normal hand is more extensive in distribution (see Figure 7.18a), with maximal significance over the central sulcus, 2 cm posterior to the location of the ipsilateral activation.

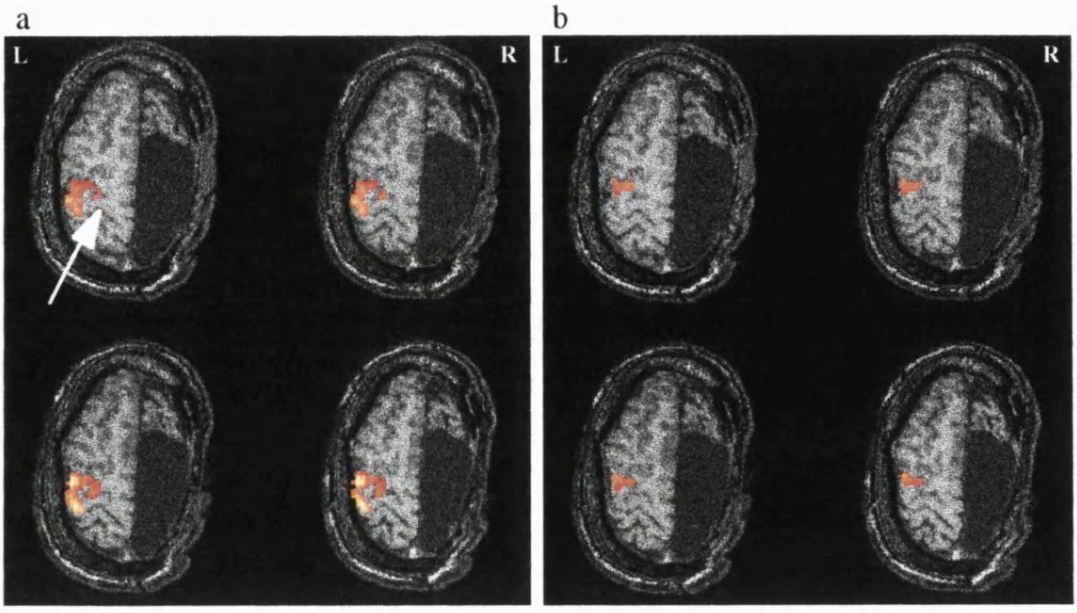


Figure 7.18: Patient 16: four adjacent axial slices over the sensorimotor cortex. Sensorimotor cortex activation (central sulcus indicated by arrow) is shown for passive movement of the normal (right) hand (a), and passive movement of the hemiplegic (left) hand (b).

Using the 3-D EPI sequence, as described in Section 3.3.1 of Chapter 3, data can be acquired to cover the whole of the head. Figure 7.19 shows the distribution of activation on passive movement of the normal (a) and hemiplegic (b) hand in patient 16 (displayed at an uncorrected p-value threshold of $p<0.01$, extent threshold $p<0.05$). Direct visual comparison revealed that, with the exception of the primary sensorimotor cortex, similar regions were activated on passive movement of the hemiplegic and normal hands. The activated regions are the primary sensorimotor cortex (normal hand only) and an immediately anterior area identified as the premotor cortex (Brodmann's area 6), the lentiform nucleus of the basal ganglia and the second somatosensory cortex (S-II) in the parietal operculum. The peak significance of the activated regions, however, differed between passive movement of the two hands. On passive movement of the normal hand, peak activation was detected in superior axial slices within the region of the primary sensorimotor cortex (this region and another in the anterior part of the S-II region achieved corrected significance ($P<0.001$)). However, with passive movement of the hemiplegic hand, the peak activation was located in the lower axial slices in the brain. In addition to an anterior region of activation in S-II similar in location to activation with the normal hand, there is also a posterior region of the S-II cortex that did not show significant activation with the normal hand (only this posterior region achieved corrected significance ($P=0.001$) with the hemiplegic hand). Figure 7.20 shows one selected slice within the region of S-II for direct comparison of the activated regions with passive movement of the normal and hemiplegic hands.

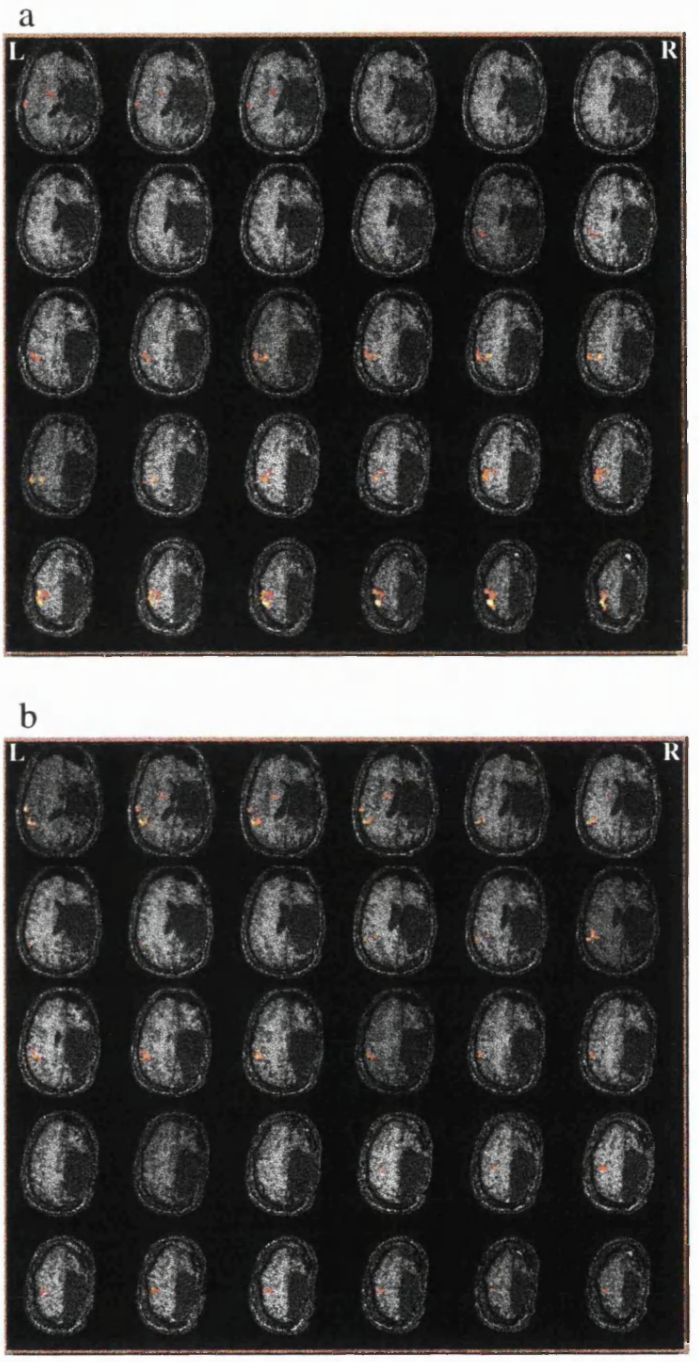


Figure 7.19: Patient 16. 30 axial slices (covering the majority of the brain) showing the distribution of fMRI activation on passive movement of the normal hand (a) and hemiplegic hand (b). (Yellow voxels more significant than red).

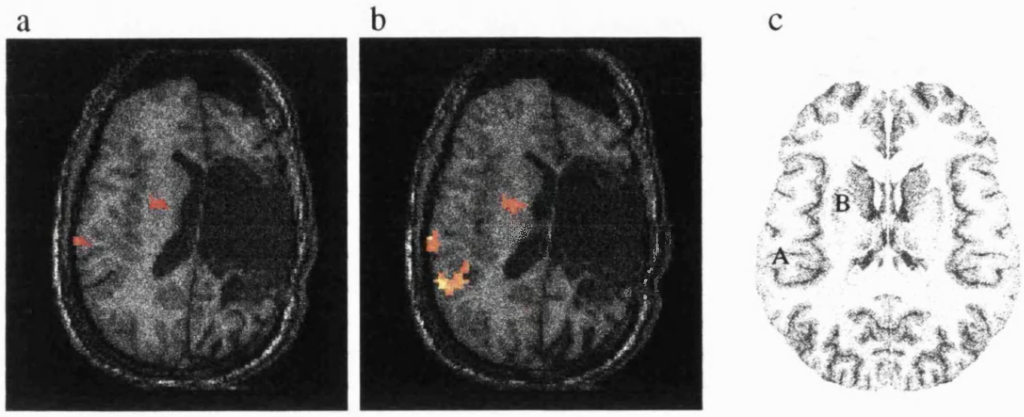


Figure 7.20: Patient 16. Comparison of activation in region of S-II on passive movement of the normal hand (a), of the hemiplegic hand (b), and a schematic (c) of the anatomical location of S-II (labelled A) and the lentiform nucleus (labelled B).

7.3.4.3 Electrical stimulation

There was no activation visible in the sensorimotor cortices following median nerve electrical stimulation of the affected side in the five patients who participated in the investigations (Patients 1, 6, 12, 15, and 17). This was either due to the dataset being rejected due to motion artefact (1 patient), or simply that there were no activated voxels detectable (4 patients).

7.3.5 Comparison between findings from different techniques within individuals

The following table (Table 7.7) summarises the fMRI, SEP and behavioural results from the 17 patients.

Subject	sex	handedess	right hand movement	left hand movement
1	male	right	c/l	c/l
2	male	right	c/l	c/l
3	female	right	c/l	c/l
4	female	right	c/l + i/l	c/l + i/l
5	female	right	c/l + i/l	c/l + i/l
6	female	right	c/l	c/l
7	male	left	c/l + i/l	c/l + i/l
8	male	left	c/l + i/l	c/l
9	female	left	c/l + i/l	c/l + i/l
10	female	left	c/l	c/l

Summary of contralateral (c/l) and ipsilateral (i/l) sensorimotor cortex fMRI activation following active movement of the left and right hand in 10 adult volunteers of left and right handedness. This Table and Table 7.7 are compared in Section 10.2 (page 247).

Patient - congenital	Residual sensory function?	Residual motor function?	Ipsilateral fMRI	Ipsilateral electrical SEPs	Ipsilateral vibration SEPs
1 (PO)	*	*	N	Y	Y
2 (AB)	* *	0	N	N	X
3 (PP)	*	0	X	N	X
4 (FC)	* *	0	Y	Y	X
5 (CB)	* *	0	X	Y	X
6 (EBa)	*	* *	N	N	X
7 (TDR)	*	*	X	Y	Y
8 (HW)	* * *	* *	X	Y	N

Patient - acquired	Residual sensory function?	Residual motor function?	Ipsilateral fMRI	Ipsilateral electrical SEPs	Ipsilateral vibration SEPs
9 (PG)	0	0	X	Y	X
10 (TB)	*	0	X	N	N
11 (RG)	* * *	0	X	Y	N
12 (PD)	0	0	N	N	N
13 (MS)	*	0	X	Y	Y
14 (BCS)	0	0	X	N	N
15 (KD)	*	0	N	Y	Y
16 (ML)	* *	0	Y	Y	Y
17 (EBr)	* *	0	N	N	X

Table 7.7: Summary of results in patients with congenital and acquired disease. 0-*** indicate the degree of residual contralateral sensory and motor function. Y (yes) indicates detectable response, N (no) indicates no detectable response, X indicates that a particular investigation was not performed. Patients who demonstrated ipsilateral fMRI and SEP responses are highlighted red, those showing ipsilateral SEP responses only are shaded blue, and those not showing ipsilateral responses using any technique are in black.

Patients with congenital disease were more likely to have residual sensory and motor function in the contralesional limb compared to the acquired group. Despite this, however, an equal number of patients from both the congenital and acquired groups demonstrated ipsilateral fMRI activation and ipsilateral SEP responses. Statistical analysis of the data in the 17 patients showed that there was no significant association between the incidence of ipsilateral electrical SEP responses and the extent of residual motor and sensory function on tapping (p=0.824; Fishers Exact Test), peg sorting (p=0.824; Fishers Exact Test), dynamometer (p=0.912; Fishers Exact Test), and double simultaneous stimulation (p=0.614; Regression Analysis). There was no significant association between the presence of ipsilateral fMRI activation and the extent of residual motor and sensory function on tapping (p=0.536; Fishers Exact Test), peg sorting (p=0.536; Fishers Exact Test), dynamometer (p=0.536; Fishers Exact Test). There was also no significant association between ipsilateral fMRI activation and double simultaneous stimulation (p=0.4; Wilcoxon-Mann-Whitney Test).

Of the 17 patients involved in the study, ten patients demonstrated ipsilateral SEP following electrical stimuli applied to the hemiplegic hand. Seven out of the ten patients also carried out vibrational SEP studies, five of whom demonstrated ipsilateral SEPs. Two out of eight patients who showed ipsilateral fMRI activation also showed ipsilateral SEPs on electrical stimulation and in the patient who also participated in vibrational SEPs ipsilateral responses were also detected. Three patients who did not demonstrate ipsilateral SEPs with vibration stimuli also showed no ipsilateral responses following electrical stimulation or fMRI. It might be expected that all of the patients who demonstrated ipsilateral electrical SEPs would also show responses with fMRI and vibration stimuli; however this was not the case. The results of the electrical and vibrational SEPs were in agreement in eight out of ten patients (five both demonstrating ipsilateral SEPs and three showing no response on stimulation of the affected side with either type of stimuli).

Of the two patients who showed fMRI activation on passive movement of the hemiplegic hand, one had acquired disease and the other had congenital disease. Similarly, there was an equal number of patients with congenital disease and acquired disease who demonstrated ipsilateral electrical SEP responses (five patients in each case). There was no significant relationship between the age of brain damage and the presence of ipsilateral electrical SEP responses (p=0.368; Regression Analysis). There was insufficient data for a statistical analysis to be performed between the age at brain damage and ipsilateral fMRI activation (only one patient in congenital and one patient in acquired group). There was also no statistically significant association between the age at surgery or the duration of epilepsy and the presence of ipsilateral electrical SEP responses (p=0.411 and p=0.66, respectively; Regression Analysis). There was insufficient data for a statistical analysis to be performed between the age at surgery or the duration of epilepsy and ipsilateral fMRI activation (only one patient in congenital and one patient in acquired group). Finally, the side of hemispherectomy was not significantly related to the incidence of ipsilateral electrical SEP (p=0.646; Fishers Exact Test). There was also no significant association between the side of hemispherectomy and the presence of ipsilateral fMRI responses (p=1.00; Fishers Exact Test).

* in the diseased brain

7.4 Discussion

7.4.1 Reorganisation of sensorimotor function

This study has demonstrated that fMRI and SEP recordings can be used to investigate sensorimotor function in patients who have undergone hemispherectomy. All of the patients examined (17 on electrical SEP, 10 on vibrational SEP, and 8 on fMRI) showed normal SEP and fMRI responses in the contralateral primary sensorimotor area when stimuli were applied to the unaffected hand, as compared to the results from control subjects described in Chapter 6. Whenever detected (i.e. in 10 of the 17 patients who underwent electrical SEP, in 5 of the 10 patients who underwent vibrational SEP, and in 2 of the 8 patients who underwent fMRI), the location of cortical responses to stimuli applied to the hemiplegic side was confined to the intact (i.e. ipsilateral) hemisphere. As described in Section 7.1.2, hemispherectomy involves the complete disconnection of one entire hemisphere. As a consequence, any residual sensory or motor function in the limb contralateral to the removed side is very likely to be subserved by the remaining ipsilateral hemisphere.

There has been much debate as to the origin of ipsilateral responses in both normal and diseased brains. In the normal brain, ipsilateral fMRI responses have only been shown to occur with active movement tasks (Li et al. 1996; Singh et al. 1998a; see Section 6.3.1.1.2 of Chapter 6). They are thought to result from ipsilateral motor and sensory pathways which abnormally persist after cortical maturation. In the case of the motor system such ipsilateral fibres may account for approximately 25% of the total ascending fibres in the normal human (for example Nyberg-Hansen & Rinvik, 1963; see Section 1.3.4.1 of Chapter 1). However, although ipsilateral fMRI responses have been shown to occur in control subjects following active movement tasks, they have not been demonstrated on passive movement tasks (Goran et al. 1996). In the present study, ipsilateral responses were demonstrated by fMRI on passive movement of the hemiplegic hand in 2 patients, although they have not been seen following passive movement of the hand in any of our adult or child controls (see Chapter 6). Isolated ipsilateral SEP responses were also seen following electrical and/or vibration stimuli applied to the hemiplegic hand in 10 patients. In these cases, the ipsilateral responses must occur as a consequence of direct ipsilateral pathways; they cannot be due to voltage spread or transcallosal pathways from the opposite hemisphere. This conclusion is consistent with that suggested in previous studies of hemispherectomised patients (for example Villanueva & Castilla, 1988). This is the first report examining the

reorganisation of the sensorimotor system using vibrational SEPs in hemispherectomised patients.

There are several possibilities as to why direct ipsilateral pathways may become more active in the diseased brain (for review, see also Section 1.5 of Chapter 1). There may be a strengthening of pre-existing ipsilateral connections present from childhood, with this strengthening promoted by functional demand (Benecke et al. 1991). Alternatively, there may be reorganisation of the ipsilateral pathway with axonal sprouting to allow a novel functional pathway (Hicks & D'Amato, 1970; Barth & Stanfield, 1990; Farmer et al. 1990). There is evidence that both of these mechanisms may exist in patients with early and late brain lesions (Carr et al. 1993; Maegaki et al. 1997). It has also been suggested that during cortical maturation through childhood, ipsilateral pathways become functionally suppressed by an inhibitory influence from the opposite hemisphere through the corpus callosum (Netz et al. 1997). This is supported by the fact that children may show associated movements until the age of about 10 years old, when callosal maturation is thought to be complete (Yakolev & Lecours, 1967; Lazarus & Todor, 1987). In addition, one study has demonstrated the presence of ipsilateral motor evoked potentials which are no longer detected after the age of approximately 10 years (Muller et al. 1997a). In patients following hemispherectomy, particularly if the hemispherectomy (or preceding brain damage) takes place early in life, such inhibition would not occur and so the ipsilateral pathways would remain functioning as the child went through cortical maturation. This might be expected to result in the patient displaying mirror movements; it may be significant that, of the patients in this study who had significant residual motor function, three out of four showed mirror movements. However, the two patients who demonstrated ipsilateral fMRI activation on passive movement of the hemiplegic hand did not display mirror movements.

There is debate in the literature as to the location of ipsilateral responses and thus how ipsilateral fibres may be organised in the primary sensorimotor cortex relative to contralateral fibres. A number of studies using different techniques have demonstrated ipsilateral activation in a similar location to, or overlapping with, the contralateral activation (see for example Benecke et al. 1991; Roth et al. 1996). This would suggest that the projections of ipsilateral and contralateral sensorimotor fibres are intermingled with each other at the level of the cortex (also suggested in a TMS study by Wassermann et al. 1994). Other studies have reported ipsilateral responses located several centimetres anterior to the peak location of the contralateral response (for example Cohen et al. 1991b; Sadato et al. 1996a; Singh et al. 1998a). Pascual-Leone et al. (1992), using TMS, found two peak locations for ipsilateral motor responses in 5 out of 7

hemispherectomised patients: one identical to, and one 2-4 cm anterior to the contralateral response. These two regions may result from two distinct pathways that may serve ipsilateral function: the uncrossed corticospinal (from the primary motor cortex) and cortico-reticulospinal (from the premotor cortex) pathways. Benecke et al. (1991) also suggested that there may be two pathways involved in ipsilateral sensorimotor reorganisation, namely that in patients with acquired disease, ipsilateral projections result from the cortico-reticulospinal pathway, whereas patients with congenital disease may show ipsilateral projections from cortico-reticulospinal or uncrossed corticospinal pathways. Both the reticulospinal and uncrossed corticospinal pathways contain fast conducting fibres and both originate from the primary motor cortex (although the reticulospinal pathway has a larger projection from the premotor cortex (Lawrence & Kuypers, 1968a; Freund, 1987, see also Section 1.3.4.1 of Chapter 1)). In the present study, both of these patterns of ipsilateral activation were demonstrated using fMRI. One patient with congenital disease showed maximal ipsilateral fMRI activation on passive movement of the hemiplegic hand that was in a similar location to the region activated in the primary sensorimotor cortex on passive movement of the normal side. A second patient with acquired disease demonstrated ipsilateral activation consistent with activation of the premotor cortex. Passive movement of the normal hand also showed activation in this region, in addition to the peak activation seen more posteriorly in the primary sensorimotor cortex. Following the hypothesis of Benecke et al. (1991), it is possible that the anteriorly located ipsilateral activation demonstrated in the patient with acquired disease may be due to activation of the cortico-reticulospinal pathway, while the ipsilateral corticospinal tract is responsible for the ipsilateral activation in the patient with congenital disease.

One patient in this study demonstrated particularly increased ipsilateral fMRI activation in the second somatosensory area (S-II) following passive movement of the hemiplegic hand. At the time of investigation, the patient had a small degree of sensory function in the hemiplegic hand, but no detectable motor function. This finding suggests that reorganisation may have occurred both inter-hemispherically (to the ipsilateral hemisphere) and intra-hemispherically (within the ipsilateral hemisphere) (this issue is further discussed in Chapter 10). Firstly, there may be inter-hemispheric reorganisation through ipsilateral pathways subserving the sensation in the hand (as mentioned previously), and secondly, intra-hemispheric reorganisation may occur within the remaining hemisphere whereby secondary sensorimotor areas have an increased role with respect to the primary sensorimotor cortex in subserving sensorimotor function. Due to the intricate network of interconnecting fibres throughout the cortex, there are pre-existing fibres between the primary somatosensory area (S-1) and S-II and between

S-II and the descending sensory pathway (see for example Burton & Robinson, 1987; Mauguiere et al. 1997). Several studies have reported that lesions occupying the whole of the hand area in S-I of monkeys resulted in the S-II area being completely unresponsive to hand cutaneous stimuli. Lesions to the S-II hand area, however, revealed no alteration in the firing pattern of the corresponding area in S-I, showing that the functional dependency of S-II on the postcentral cortex is not reciprocal (Pons et al. 1987; Burton et al. 1990; Garraghty et al. 1990, 1991; Pons et al. 1992) strengthening the evidence for the serial processing of somatosensory information. MEG studies have revealed a sequential activation of cortical areas during processing of afferent sensory inputs, suggesting a hierarchical and a serial organisation between areas S-I and S-II (Hari et al. 1983; Forss et al. 1995; Mauguiere et al. 1997). Contradictory evidence in animals, however, has shown no evidence of major changes in the responsiveness or function in S-II following deactivation of S-I (Turman et al. 1992; Zhang et al. 1996), suggesting that the S-I area may have only a background facilitatory influence on the function of S-II. In fact, S-II is thought to represent the body bilaterally in the normal human (for example Richer et al. 1993; Forss et al. 1994b; see Section 1.4.2 of Chapter 1). It appears unlikely therefore that axonal sprouting is entirely responsible for such reorganisation of the input/output connections to S-II, but rather a strengthening of the fibres already present. There has been a small number of previous brain mapping studies demonstrating ipsilateral pathways in association sensorimotor cortices in hemispherectomised patients. Recently, Graveline et al. (1998) showed ipsilateral fMRI activation in the premotor and SMA in patients following hemispherectomy. Several PET studies have also shown similar ipsilateral non-rolandic areas to be activated on stimulation of the hemiplegic side (for example Muller et al. 1997b, 1998; Toussaint et al. 1997; Nariai et al. 1999). However, none of these studies have reported an increased role for the ipsilateral S-II area in the reorganisation of sensorimotor function in hemispherectomised patients.

Behavioural measures of motor function revealed that four of the 17 patients were able to move their contralesional hand; however, none of these patients were able to perform individual finger movements. Previous literature has suggested that individual finger movements requires direct corticomotoneuronal projections, which for distal muscles terminate mainly contralaterally (Kuypers & Brinkman, 1970; Kuypers, 1981; Passingham, 1993; Porter & Lemon, 1993). Indeed, lesion studies in the monkey suggest that the ability to make individual finger movements depends on the integrity of crossed corticospinal pathways and the contralateral sensorimotor cortex (Passingham et al. 1983). The inability of hemispherectomised patients in the current study to perform

contralateral finger tapping or peg sorting corroborates the necessity of the contralateral cerebral hemisphere for individual finger movements.

7.4.2 Factors affecting brain reorganisation

As expected from previous literature (for example Gardner et al. 1955), patients with congenital disease showed better residual sensory and motor function in the hemiplegic limb when compared to patients with acquired disease. Such function, however, was not found to significantly correlate with the incidence of ipsilateral responses demonstrated with fMRI or SEP recordings. It is interesting that the patients with the greatest amount of residual function did not necessarily demonstrate ipsilateral responses, and that patients who demonstrated residual sensory but no motor function also showed ipsilateral SEP and fMRI responses. In one case, ipsilateral SEP responses following electrical stimuli were seen even though the patient displayed no residual sensory or motor function in the hemiplegic hand. (It should be noted, however, that the absence of detectable ipsilateral activation in patients with brain lesions does not necessarily mean that there is no neuronal activity in the appropriate region, since it may be below the level of sensitivity of the techniques used for investigation). In this study, residual sensory or motor function appears therefore not to be a pre-requisite for ipsilateral cortical sensorimotor activation using fMRI and SEPs. In contrast, previous literature has generally shown a correlation between residual sensorimotor function and the presence of ipsilateral activations (for example Benecke et al. 1991; Muller et al. 1997b Nariai et al. 1999). However, there have been few studies examining the relationship between residual sensorimotor function and the presence of ipsilateral responses in hemispherectomised patients, and to date no studies have been carried out using fMRI or SEP methods. Nariai et al. (1999), using PET, suggested that cortical reorganisation in the undamaged hemisphere may have a significant role in preserving residual motor function in the ipsilateral limb. Pascual-Leone et al. (1992) reported using TMS that, in five out of seven hemispherectomised patients, better motor functional outcome was associated with the presence of ipsilateral projections that were topographically different from normal, and their location may depend on the age at the time of hemispherectomy and the time elapsed between surgery and testing. Several investigations in patients with other brain lesions (for example infarcts affecting the middle cerebral artery territory), have also suggested that the better the extent of residual function, the more likely the incidence of inter-hemispheric reorganisation through ipsilateral pathways (for example Chollet et al. 1991; see Chapter 8); however, this is still debated (Turton et al. 1996).

In contrast to many previous studies in patients with brain lesions, including hemispherectomised patients (Benecke et al. 1991; see Section 1.5 of Chapter 1), the present study showed no significant relationship between the presence of ipsilateral SEP and fMRI activations and the age of brain damage. This may be explained by a number of factors. Firstly, all the children studied had their first seizure at the age of 8 years old or younger. This is particularly significant given the findings of Muller et al. (1997a) suggesting that cortical maturation occurs around the age of 10 years. Cortical damage sustained before this time could effectively result in reorganisation of the sensory and motor pathways before 'hard-wiring' and cortical maturation is complete. In addition, several studies have suggested that the age at surgery or the duration of epilepsy influences reorganisation of sensory and motor function (for example Beckung et al. 1994). There was no significant relationship between the presence of ipsilateral SEP and fMRI activations and the age at the time of hemispherectomy surgery or the duration of epilepsy. As may be seen from Table 7.2, the mean age at which the patients had their surgery was similar for the groups with congenital and acquired disease, which may explain our findings. The present study, although involving large numbers of patients relative to previous reports, nevertheless is based on a number that is small with respect to further statistical analysis. In order to make significant interpretations of the effect of age of onset of disease, age at surgery and duration of epilepsy, a greater number of patients with both congenital and acquired disease are required, with a larger variation in the age of onset of the disease, duration of epilepsy and age at surgery.

7.4.3 Methodological issues

Many studies have made an association between the activation found in the ipsilateral (as well as contralateral) primary motor cortex and the presence of mirror movements (for example Cohen et al. 1991c; Weiller et al. 1992; Weder & Seitz, 1994). In addition, several studies have reported mirror movements present in patients who have undergone hemispherectomy (Ueki, 1966; Muller et al. 1991; Dijkerman, 1996). Weder & Seitz (1994) suggested that the effort of the patient to move the fingers of the affected hand resulted in associated movements and a bilateral activation of the motor cortex. This raises the possibility that ipsilateral activations might in fact be due to additional contralateral movements and represent an epiphenomenon. In this study, passive movement was carried out during fMRI investigations which did not involve active patient participation. All patients were assessed before the fMRI examination to ensure that they could allow one hand to be moved without moving the contralateral hand. In addition, during the session the contralateral hand was positioned so that it could be seen by the examiner to ensure it was not moving. One patient (patient 6) did have

demonstrable mirror movements, but it was possible to move the hemiplegic hand passively with no visible movement in the normal hand. In fact, this patient did not demonstrate ipsilateral activation on passive movement of the hemiplegic hand with fMRI, thereby providing support for the view that increased ipsilateral sensorimotor cortex activation on movement of the hemiplegic side is not a result of simultaneous contralateral movement of the unaffected hand. In addition, none of the patients who demonstrated ipsilateral fMRI activation on passive movement of the hemiplegic hand had mirror movements. For all SEP recordings performed in this study, interaction between hands was prevented by ensuring the patients hands were kept apart throughout the session, so that the stimulus could not be felt in the other hand.

A further potential source of ipsilateral activation on fMRI is movement of the ipsilateral shoulder during the hand movement task, since the proximal muscles of the limbs have bilateral cortical representation (Colebatch et al. 1991). However, as emphasised above, the motor task performed in the present study consisted of passive movement of the patient's hand, which minimises the potential for involvement of remote muscle activity; it should be noted in this context that none of our control studies, performed using the same passive task, showed any evidence of ipsilateral activation on fMRI (refer to Chapter 6).

The present study has suggested that with both electrical and vibration stimuli there appears to be a significant increase in latency and decrease in amplitude of the components on stimulation of the ipsilateral (hemiplegic) compared to the contralateral (unaffected) side. This finding is in agreement with several previous studies (for example Hazemann et al. 1969; Villanueva & Castilla, 1988; refer to Section 7.1.4.1). In contrast, several studies have shown no ipsilateral cortical responses following SEP recordings in the intact hemisphere (Stohr & Goldring, 1969; Noel & Desmedt, 1980; Dijkerman et al. 1993). However, it should be noted that in some cases in this study it was difficult to identify comparable SEP components between the ipsilateral and contralateral responses. Therefore, it is unclear whether individual components of the ipsilateral SEP waveform are actually delayed compared to those observed in the normal SEP response (from stimulation of the normal hand) or separate components entirely (unique to the ipsilateral response). As a result, one cannot assume the contralateral and ipsilateral components selected are subserved by the same somatosensory pathway.

7.5 Conclusions

In this study, ipsilateral sensorimotor cortex activation has been demonstrated using fMRI and SEP recordings in a number of children following hemispherectomy surgery. Ipsilateral responses were seen most often using SEP recordings using electrical stimulation (10 out of 17 patients). Ipsilateral responses were also observed with vibrational SEPs (5 out of 10 patients) and fMRI following passive movement of the affected hand (2 out of 8 patients). Behavioural measures at the time of the investigation revealed that 14 out of 17 patients had residual sensory function in the affected upper limb and 4 of these patients also had residual motor function in the limb. The location of the ipsilateral primary sensorimotor fMRI activation was similar to that found on movement of the normal contralateral side. In addition, the results for one of the patients suggest a relatively greater role for the secondary somatosensory area for movement of the hemiplegic hand than for movement of the normal hand. Ipsilateral sensorimotor responses were demonstrated in patients with both congenital and acquired disease, and there was no significant association found between ipsilateral fMRI or SEP responses and the age of brain injury. This study has therefore suggested that factors additional to the age at injury may influence cerebral reorganisation. In addition, there was no significant relationship between ipsilateral responses and residual sensorimotor function.

Chapter 8: Reorganisation of sensorimotor function in children following vascular damage to the middle cerebral artery territory.

8.1 Introduction

8.1.1 Aims of this study

Although stroke represents a serious public health concern, nevertheless by studying patients who have sustained damage as a result of impaired cortical and subcortical circulation, it has been possible to infer the contributions of various brain regions to normal cerebral operations and to explore the adaptation of remaining tissue to selective neuronal loss (for example Chollet et al. 1991). In addition, inquiries into the mechanisms underlying observed recovery of function have led to improvements in the methods and timing of rehabilitation in stroke patients (Liepert et al. 1998).

The aim of the present study was to examine, using fMRI, SEP and behavioural techniques, a group of patients who had suffered sensorimotor deficits as a result of discrete brain lesions (as compared to Chapter 7, where similar studies were performed on patients with complete disconnection of an entire hemisphere as a result of hemispherectomy surgery). Using these techniques, the reorganisation of sensorimotor function was investigated and related to functional recovery, age at insult, and location of lesion.

8.1.2 The terminology of stroke

An ischaemic or haemorrhagic insult to the brain will often result in tissue damage, with the consequence that the patient may experience a neurological deficit. The term 'stroke' is used to refer to the clinical syndrome of permanent neurological deficit of vascular origin, and is distinguished from transient ischaemic attack (resolution of symptoms and signs within 24 hours) and reversible ischaemic neurological deficit (resolution beyond 24 hours) (Kirkham, 1999). Stroke is a common disease in adulthood, and it also occurs in children, although with a much reduced incidence (affecting approximately 2.6 and 3.1/100 000 white and black children, respectively) (Broderick et al. 1993). The

aetiology of childhood stroke is uncertain in many cases, with a large proportion of cases having cerebrovascular disease. Some groups of children may be at particular risk, such as those with sickle cell disease, congenital heart disease and cranial trauma (Golden, 1985; Giroud et al. 1997, for review see Kirkham, 1999). In general, survival rates and functional recovery rates are better in children than in adults following stroke (Giroud et al. 1991).

Before discussing the aims of this chapter (refer to Section 8.1.1), firstly a review is given of the literature on the reorganisation of sensory and motor function in stroke patients (see below). The studies are grouped according to the technique used, with particular emphasis on studies using fMRI, SEPs and behavioural measures which are pertinent to this study. Most of these studies have been carried out in adult stroke patients. To date, there are only a few studies investigating sensorimotor function after stroke in children.

8.1.3 Reorganisation of sensorimotor function following stroke

Hemiparesis is the most common deficit after stroke, affecting more than 80% of patients acutely and more than 40% chronically (Gresham et al. 1995). Until recently, it has been commonly believed that once an area of brain has been infarcted or otherwise damaged there is little or no potential for functionally effective regeneration or replacement of lost neurones. Despite this, the majority of patients who survive an acute stroke do show some evidence of improvement over time, and in some cases there may be quite remarkable recovery of function from what initially appeared to be an incapacitating hemiplegia. Early recovery during the first few days following an ischaemic insult is likely to be due to factors such as resorption of oedema, or opening of collateral channels for circulation to the damaged region (Goldstein & Davis, 1990). But late recovery - after the first 3 to 4 weeks - is more likely to be due to other mechanisms of neuroplasticity which may go on for several months (Goldstein & Davis, 1990). Such mechanisms could include axonal sprouting, the formation of new synaptic connections, or the unmasking/disinhibition of pre-existing, unused pathways (see review in Section 1.5 of Chapter 1). It is such plasticity underlying altered behaviour and cortical activity after stroke that is investigated in this study.

There may be several mechanisms underlying functional sensorimotor reorganisation (for a more detailed review, see Section 1.5 of Chapter 1). In some situations, functions may be reorganised to immediately adjacent functionally related areas of cerebral cortex

(Maegaki et al. 1995). In other cases, reorganisation of function may occur to more remote sites in the same hemisphere, or perhaps even to the undamaged contralateral hemisphere (for example Fries et al. 1993; Chollet et al. 1991). When large areas of cortex are damaged, there may not be sufficient surviving tissue around the affected site to allow cortical reorganisation in close proximity to the lesion. In these situations, it is thought more likely that representations will shift to areas which are closely related functionally but which may not be in close physical proximity. That is, a shift in the hierarchical organisation of the system may occur. For example, nonprimary cortical motor areas and their efferent corticocortical and corticosubcortical pathways may compensate for disruption of the output of the primary motor cortex (Weiller et al. 1993). This is theoretically possible because of the large number of parallel and independent inputs to and outputs from the motor and sensory cortices, as described in Chapter 1. Indeed it has been suggested that higher-order areas of the sensorimotor cortex have a greater capacity for reorganisation than do primary areas (Pons et al. 1988). Evidence also exists for the role of uncrossed, ipsilateral sensory and motor pathways in enhancing the recovery of function; however, this is still debated as studies of the role of ipsilateral pathways in functional cortical reorganisation after stroke have reported a high degree of inter-subject variability (Netz et al. 1997).

Ischaemic lesion studies in animals have also contributed to our understanding of cortical plasticity and recovery of function. In a study by Nudo et al. (1996), squirrel monkeys were trained in skilled motor movements required to retrieve food pellets from small wells. After completion of the training, motor cortex maps were derived by intracortical microstimulation techniques. Focal infarcts of the cortical motor hand area were then induced by electrocoagulation of the blood vessels supplying this zone where the vessels entered the cortical surface. Within 5 days of surgery, the monkeys were started on a retraining protocol identical to that preceding the infarct. Initially, hand skill was markedly reduced, but after 3-4 weeks of retraining, preinfarct performance levels were attained. Motor cortex mapping was repeated, and it was found that hand representations had invaded adjacent regions formerly representing elbow and shoulder. These results were contrasted with a study of spontaneous cortical reorganisation in monkeys with similar infarcts (but without motor skill training), in which there was no reappearance of movements represented in the surrounding cortex of the infarcted zone (Nudo & Milliken, 1996). Instead, there was a further loss of cortical hand representation in adjacent spared cortex, perhaps because of diminished use of the affected hand. These two studies suggest that rehabilitation therapy prevented further loss of hand representation in intact cortex, and induced expansion of hand territory into adjacent cortical areas, in association with recovery of skilled movement. A more recent study in

monkeys has shown somatosensory cortex plasticity within the damaged hemisphere, visible as either the re-emergence of existing areas, an enlargement in existing areas, or the appearance of new areas (Xerri et al. 1998).

Although the timing and extent of motor recovery may vary for individual patients, several studies have indicated that most functions either re-emerge in a short period of time or remain permanently lost. The time for full recovery has been shown to vary between 8 weeks and 6 months after the insult (Andrews et al. 1981; Atilbeck et al. 1983; Bonita & Beaglehole, 1988). Several factors may predict recovery. Most importantly, improvement seems to be more likely when initial deficits are limited (Bonita & Beaglehole, 1988). In addition, the extent of recovery is often greater when early impairment resolves quickly (Duncan et al. 1994). Gender and age, on the other hand, do not appear to reliably predict recovery (Bonita & Beaglehole, 1988; Freund, 1997). A recent study has evaluated the relationship of morphological and CBF patterns to both the severity and the evolution of the motor deficit following stroke (Pantano et al. 1996). The eventual degree of motor recovery (examined over a period of 3 months) was negatively correlated with the time from the stroke until entry into the study, but not with the severity of neurological impairment at the time of entry into the study. In addition, the volume, side, and location (cortical or subcortical) of the infarct did not correlate with either the severity or evolution of the motor deficit. As the findings of these studies suggest, it is difficult to accurately predict functional outcomes in individual patients (Dombovy & Bach-y-Rita, 1988).

8.1.3.1 SEP studies

There have been a number of SEP studies using electrical stimulation in patients who have had ischaemic insults (for example Pavot et al. 1986; Tsuji et al. 1988; Kato et al. 1991; Yamamoto et al. 1995). Most have concentrated on the relationship between the locus of the stroke and the presence of early latency components in the SEP. Many of these studies have also examined the relationship between functional sensory impairment, stroke location and electrical SEP findings (for example Pavot et al. 1986; Kato et al. 1991; MacDonell et al. 1991).

A major feature associated with early SEP studies in patients with vascular events such as stroke was a decrease in the amplitude and an increase in the latency of the cortical SEP observed on electrical stimulation (for example Williamson et al. 1970; Tsumoto et al. 1973; Regli & Despland, 1982; Stejskal & Sobota, 1985). More recent studies have

related the location of brain damage to the SEP abnormality. Yamamoto et al. (1995) found that the N20 was absent or its amplitude reduced in all patients with lesions in the putamen or posterior thalamus, but was normal with lesions in the posterolateral portion of the thalamus or the corona radiata (which excludes thalamic fibres). Similarly, in a group of patients with thalamic or putaminal haemorrhage lesions, Kato et al. (1991) found abnormalities in the median nerve SEPs of 92% of patients. In contrast, a more recent study investigating patients with ischaemic lesions showed abnormal somatosensory evoked field responses which showed no apparent relationship with the location of the lesion (Rossini et al. 1996). Similarly, Seitz et al. (1998) reported a reduction in the amplitude of the N20 component, with no changes in latency or correlations with lesion size, in a group of 7 patients with middle cerebral artery infarction. These patients had all suffered from an acute severe hemiparesis, but had subsequently shown marked improvement in the functional abilities of their hand.

There are further contradictory reports in the literature regarding the relationship between the loss of specific components of the SEP and the patients' functional sensorimotor deficit or the location of the ischaemic lesion (Mauguiere et al. 1983; Mauguiere & Desmedt, 1991). Some studies have found that patients with a hemiparesis but normal sensory function did not show precentral P22 and N30 SEP components and that the parietal components N20 and P27 were preserved. In patients with a clinical sensory loss which is unaccompanied by a central motor impairment, these precentral components were preserved but the parietal SEP components were lost. However, a study by Tsuji et al. (1988) reported the opposite loss of components related to functional outcome in a group of patients with pre- and postcentral lesions. The precentral P22 and N24 SEP components were absent in patients with postcentral lesions and displaying hemianaesthesia but preservation of muscle strength, which they suggest indicates that sensory input to the precentral areas was damaged. On the other hand, N20, P20 and P23 components were normal in patients with pure motor hemiplegia or hemiparesis due to precentral lesions. Similarly, Robinson et al. (1985) found that the N20/P23 components appeared to be normal in patients with a pure sensory stroke and normal CT reports, while patients with pure sensorimotor strokes with infarcts in the thalamus and posterior limb of the internal capsule showed abnormal N20/P23 responses. Franssen et al. (1992) also reported a reduction or absence of SEP components in patients with a variety of subcortical infarcts and somatosensory or sensorimotor deficits, but normal SEPs in patients with subcortical infarcts and a pure motor deficit. Such lesion studies may provide valuable information into generator sites for SEP components and the anatomical segregation of neuronal pathways between the sensory and motor cortex and subcortical structures.

Despite this literature on the characterisation of the SEP following ischaemic insults, there has been little evidence from SEP recordings to support the role of ipsilateral pathways in the reorganisation of function. One early study reported that, in patients with damage to the middle or internal carotid artery territory, the presence of an ipsilateral response was entirely dependent on there being a contralateral response (Kuksova & Sumskii, 1983). They suggested that the ipsilateral response could not be generated independently, in agreement with studies in normal controls (see Section 6.3.1.1.2 of Chapter 6). In addition, in an SEP study of adult patients with an acquired unilateral brain lesion, contralateral N1 (peak latency 19 ms) responses were observed to stimulation of the affected side in patients with normal sensory function; however, they were reduced or absent when the patient had sensory loss (Tsumoto et al. 1973). They also reported that ipsilateral N1 responses could not be elicited in either patient group.

8.1.3.2 fMRI studies

There have been few fMRI studies investigating motor recovery after stroke. In a study by Cao et al. (1998), eight patients recovering from hemiparesis or hemiplegia carried out a sequential finger to thumb opposition task. The patients had suffered a single unilateral ischaemic stroke in different locations, both cortical and subcortical. Group results showed that, with movements of the paretic hand, the volume of activated ipsilateral sensorimotor cortex was more extensive in six of the eight stroke patients than in control subjects. Bilateral activation of the primary sensorimotor cortex was recorded in three of the patients in whom the infarct had spared the hand area of the primary motor cortex. The remaining three patients had suffered infarctions in the precentral gyrus and showed ipsilateral activation alone. Only two of these six patients were reported to have mirror movements (one patient with bilateral activation and one with ipsilateral activation only). This study also demonstrated the involvement of ipsilateral secondary association areas following unilateral stroke. Two patients also demonstrated extended areas of activation in the ipsilateral premotor and dorsolateral prefrontal cortex when compared with control subjects (in addition to ipsilateral primary sensorimotor cortex activation). Finally, in two patients with frontal infarctions, activation in the ipsilateral supramarginal gyrus and in the ipsilateral premotor cortex, as well as the primary sensorimotor cortex, was observed during paretic hand movements. The insula gyrus, thalamus and cerebellum were not imaged in the study.

Cramer et al. (1997), like Cao et al. (1998), also performed an fMRI study to compare brain activation in normal controls and patients who had recovered from hemiparetic stroke. In this study, 10 patients were examined, 5 with deep and 5 with cortical infarcts, and brain activation was achieved by an index finger tapping task (one subject was excluded because of excess head motion). They found that stroke patients activated the same cortical regions as controls; however the activated regions were often larger in the patients than in controls. As in the study by Cao et al. (1998), ipsilateral sensorimotor cortex activation on movement of the recovered hand was greater in over half of the stroke patients (6 out of 9) than in the controls. In a subset of these 6 patients, increased activation was also seen in the contralateral cerebellum, ipsilateral premotor, bilateral supplementary motor cortices and also along the rim of the cortical infarct. The authors also suggest that some of the peri-infarct activations may reflect cortical motor map reorganisation similar to that described in monkeys (for example Nudo et al. 1996). In addition, they discovered that during finger-tapping of the unaffected hand in stroke patients, decreased activation was seen in the unaffected contralateral sensorimotor cortex (Cramer et al. 1997). This finding suggests that the normal sensorimotor region is differentially responsive to contralateral and ipsilateral hand movement, with an increased response to ipsilateral hand movement and a decreased response to movement of the contralateral hand. Interestingly, in rats subjected to a unilateral sensorimotor cortex lesion, immobilisation of the unaffected forelimb for the first 15 days prevented dendritic growth and produced severe, lasting deficits in the impaired forelimb (Kozlowski et al. 1996). Together, these observations suggest that during recovery from stroke, unaffected limb activity drives neuronal changes in the unaffected sensorimotor cortex which may be associated with recovery of the affected limb. However, after recovery has reached a plateau, the unaffected limb activity produces an attenuated response in the unaffected sensorimotor cortex, in association with an increased response to affected limb activity. Similar studies have been carried out in humans. Taub et al. (1993) reported that constraining the upper extremity of the unaffected limb resulted in long-term improvement of motor function in the impaired limb.

Another study has examined a group of 24 patients with more general neurovascular lesions, including a subgroup with ischaemia (Schlosser et al. 1997). The fMRI results that were obtained appeared to correlate with the functional deficit following the insult. Reorganisation of cortical functional areas was seen: both intrahemispheric with 5 patients showing activation at a different anatomic locale (6 patients also showed anatomical displacement of the activated cortex most likely due to a mass effect of the lesion), and interhemispheric with 3 patients demonstrating bilateral activation on movement of the defective hand. In the latter group of patients, hemispheric symmetry

was seen in the location of the activated cortex, but there was marked asymmetry in the number of activated voxels between the affected and unaffected hemispheres (only a few activated voxels detected in the affected hemisphere). A further fMRI, MEG and TMS study of a single patient with excellent motor recovery following a fronto-parieto-temporal stroke consistently demonstrated an asymmetrical enlargement and posterior shift of the sensorimotor areas in the affected hemisphere (Rossini et al. 1998).

There are a number of additional preliminary fMRI reports (in conference presentations) of patients with ischaemic strokes that have documented activation of alternative motor patterns to those seen in normal controls. McIntyre et al. (1997) found two patterns of activation in two patients who had recovered from stroke, one of extensive ipsilateral activation in the prefrontal and premotor cortices, and the other showing activation surrounding the damaged area within the motor cortex. These two patterns of reorganisation were also seen in a study by Binkofski et al. (1999), but they correlated with lesion location. Increased ipsilateral supplementary motor area (SMA), premotor area (PMC) and posterior parietal cortex (PPC) activation (and contralateral primary sensorimotor cortex activation) was found in patients with lesions confined to the premotor or parietal association cortex, or with subcortical lesions. Patients with lesions in or around the primary sensorimotor area showed perilesional activation of the primary sensorimotor cortex in the subacute stage of recovery; however, at a later stage this activity was not found, but additional activation of the SMA, PMC, PPC, and the ipsilateral primary sensorimotor cortex was present in many cases. Several studies have demonstrated enhanced ipsilateral hemisphere activation in the precentral gyrus and anteriorly in Brodmann's area 6 (premotor cortex) compared to controls (Presciutti et al. 1996, 1998). Premotor cortex activation was predominantly seen in patients with no residual motor impairment and ipsilateral precentral gyrus activation found in patients with a motor deficit. Recently, Hernandez et al. (1999) demonstrated the recruitment of the ipsilateral hemisphere in the early (less than 5 days post-stroke) but not chronic (greater than 1 month post-stroke) stages of stroke recovery. The authors suggested that the ipsilateral cortico-spinal tract was activated because of the greater difficulty in performing the task.

8.1.3.3 Behavioural tests

It is well recognised that damage to the primary or secondary sensorimotor cortices often results in a reduction or loss of contralateral voluntary motor control and sensory perception. Behavioural studies in lesioned animals and in man have demonstrated the

extent of these impairments and the subsequent recovery of function (for example Glees & Cole, 1952; Rudel et al. 1974; Marque et al. 1997; Xerri et al. 1998). A detailed study by Marque et al. (1997) of 15 patients with hemiplegia with lesions in various locations, showed the existence of significant deficits of motor function in the limb contralateral to the lesion 20 days following the episode. Force (tested using hand grip and isokinetic movements) and dexterity (nine hole peg test) were mainly impaired, whereas repetitive movements (finger tapping) were spared. When re-tested 90 days after the insult, the motor impairment had recovered to almost completely normal levels, although the nine hole peg test results were still significantly different from controls. However, many reports have accumulated findings of poor motor outcome following capsular and striatocapsular strokes (for example Fisher, 1979; Rascol et al. 1982; Donnan et al. 1991). Fries et al. (1993) assessed residual motor function in 23 patients following capsular or striatocapsular stroke and found specific motor deficits corresponding to particular locations of lesions. Lesions in the anterior or posterior limb of the internal capsule led to an initially severe motor impairment which was followed by excellent functional recovery. On the other hand, lesions of the posterior limb of the internal capsule in addition to damage to the lateral thalamus compromised motor outcome. Caudate and putamen lesions in isolation did not affect motor control. Single case studies of patients with discrete cortical infarctions localised to the posterior bank of the precentral gyrus have shown a predominant thumb flexion weakness (Terao et al. 1993) or isolated weakness in the fingers, specifically in thumb adduction (Lee et al. 1998). Only one of these studies reported motor recovery to normal levels three months after the stroke (Lee et al. 1998).

The presence of mirror movements has been suggested to reflect the altered activity in the unaffected hemisphere (Weiller et al. 1993; Leonhardt et al. 1997), and recently has been related to the degree of motor deficit following a stroke (Nelles et al. 1998). In the latter study, mirror movements in the unaffected hand (with movement of the paretic hand) were observed more often in patients with greater motor deficits, while the incidence and magnitude of mirror movements in the paretic hand (with movement of the unaffected hand) more closely resembled results of control subjects. The authors suggest that the observation of unaffected hand mirror movements in subjects with greater motor deficit may represent a clinical sign of restorative processes after a unilateral stroke.

Ipsilateral motor deficits have also been reported in patients with hemispheric lesions using a variety of behavioural tests (Vaughan & Costa, 1962; Wyke, 1971; Finlayson & Reiten, 1980; Jones et al. 1989; Marque et al. 1997). Brodel, in his self report (Brodal, 1973), described difficulty with writing and other fine motor tasks with his right hand

following a right hemisphere stroke. Jones et al. (1989) found significant impairment of ipsilateral sensorimotor functions measured with computerised tracking tasks in patients with unilateral cerebral infarctions, although there was only marginal impairment in grip strength. Another study, however, has also shown conflicting results with no significant impairment in the supposed normal side (Haaland & Delaney, 1981). Collectively, these studies raise the question of the involvement of ipsilateral pathways in recovery of motor function in both adults and children (Marque et al. 1997).

8.2 Methods

Eleven patients took part in the study (6 females and 5 males). Their ages ranged from 8.8 to 22 years (mean 14.5 years). Nine patients were selected who had suffered from a middle cerebral artery occlusion and had a prolonged sensory or motor deficit following the insult. All of these patients were investigated at least 6 months following the insult. In addition, two patients were studied who had congenital brain lesions. As with the control subjects described in Chapter 6 and the study of hemispherectomised patients in Chapter 7, all patients underwent investigations of both 'normal' and 'impaired' hands. In these studies the ipsilesional 'normal' hand functions as a direct control for the impaired side.

8.2.1 Behavioural tests

Behavioural assessments of sensory and motor function were carried out in all patients, as described in Chapter 5.

In order to grade residual motor function in the affected hand, an average value was calculated from the patients' performance on the peg sorting, force production (dynamometer), and finger tapping tests. Expressed as a percentage of the score achieved with the unaffected hand, a performance of greater than or equal to 80% was designated as normal function (****), 60%-79% was designated as mild deficit (***), 30%-59% was designated as moderate deficit (**), detectable function up to 30% was designated as severe deficit (*), and 0% was designated as no detectable function (0).

The patients' residual sensory function in the affected hand was graded according to their performance in the test of double simultaneous stimulation (the test of joint position sense was performed in only 6 of 11 patients, and therefore could not be used in the

classification of patients' sensory function). A score of greater than or equal to 80% correct responses was designated as normal function (****), scores between 60%-79% were designated as mild deficit (***), 30%-59% correct were designated as moderate deficit (**), 1%-29% correct were designated as severe deficit (*) and 0% was designated as no detectable function (0).

8.2.2 SEPs

The method and stimuli details used to record electrical and vibrational SEPs are described in Section 4.2 of Chapter 4. Ten out of eleven patients underwent SEP investigations using electrical stimuli above motor threshold (M+S intensity) and using vibration stimuli. SEP recordings were taken on stimulation of the 'normal' and 'impaired' hand; a schematic representation of the montage that was used is depicted in Figure 8.1. Recordings were taken from a total of 62 electrodes, with the majority of electrodes located over the sensorimotor cortices of both hemispheres. All averages were referenced to three frontal electrodes over the hemisphere ipsilateral to the side of the stimulus.

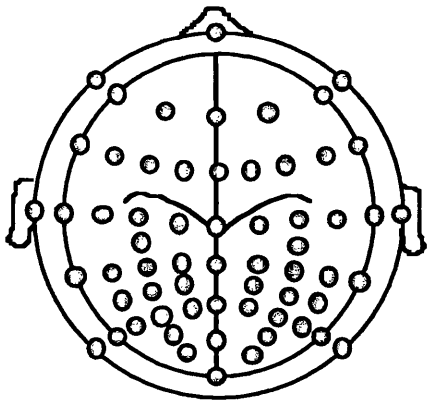


Figure 8.1: Schematic representation of the montage used in this study. Electrodes shaded red indicate those used to display waveforms (see Section 8.3.2).

Waveforms and voltage maps were obtained for stimulation of the normal and affected side. Latencies and amplitudes of the first negative and positive components (known as the N20/P30 and N30/P40) were compared for the normal and affected hand (see Section 4.2.2 of Chapter 4). Paired t-tests were performed for comparison between contralateral and ipsilateral measurements.

8.2.3 fMRI

All 11 patients underwent fMRI investigations. It has been previously shown in this thesis that active movement produced a greater percentage signal change in the contralateral sensorimotor cortex than passive movement, which approached a statistically significant difference (see Section 6.3.1.1.1 of Chapter 6). Therefore, it was decided in this group of patients, the particular hand sensorimotor task that was performed was decided on the ability of the patient to move the affected hand, and where possible an active movement task. The active movement task consisted of the patient moving his/her fingers, in unison, in and out of the palm of the hand. As with the hemispherectomised patients undergoing fMRI investigations (Chapter 7), passive movement was performed by the examiner moving the patients' fingers in and out of the palm with each hand, with a flexion/extension movement of the metacarpophalageal joints. Both passive and active hand movements were performed at a rate of approximately 2 Hz. While the patient lay in the scanner, the elbow was supported with light padding on both sides or through the use of an arm rest, both for comfort and to raise the hand slightly to assist the examiner in reaching the hand if necessary.

A total of 120 3-D datasets were collected, divided into 12 task/rest cycles with 5 datasets in each state. The collected images were realigned and analysed using SPM, as described in Section 3.2.1 of Chapter 3. Activation maps were spatially smoothed to three times the original voxel size. *P*-values are reported as uncorrected or corrected for multiple comparisons.

8.2.4 Statistical Analysis

Statistical analyses were carried out on the fMRI and SEP data in relation to the behavioural test results (using the raw data for each of the tests), age at injury, site of brain damage, shift in handedness due to insult, and handedness at the time of testing. The results obtained from the statistical analyses are included for completeness, recognising that these lack power due to the small sample size used in this study. For the behavioural test results, ipsilesional observations were used as an index of inherent performance. Given that the range of values obtained from the ipsilesional observations was generally small compared with the range of contralesional values, the ratio of the two observations was used as a response variable, thus providing a simple adjustment for inherent performance. Examination of the response data showed three different

categories of distribution behaviour. Accordingly, one of the following statistical analyses were performed as appropriate.

Category 1: In those cases in which the observed value of the dependant variable is mostly zero with some non-zero values then a binary response variable (zero or non-zero) was generated, forming a 2x2 contingency table. Given the small frequencies involved, Fisher's Exact test was used.

Category 2: Those not belonging to category 1, but in which the identical distribution assumption could not be invoked, Wilcoxon-Mann-Whitney test was used as a test of association (as opposed to its usual use as a test of the equality of 2 medians).

8.3 Results

The details of the patients are summarised in Table 8.1. The patients numbered 1, 2, 3 and 4 had both cortical and subcortical infarcts. Patients 5, 6, 7, 8 and 9 had infarcts of the basal ganglia and adjacent white matter only. Patients 10 and 11 did not have infarcts. Patient 10 had cortical dysplasia and patient 11 had a neuronal migration defect. All patients underwent fMRI and behavioural investigations. One patient (patient 9) was unable to participate in SEP recordings.

patient	age at insult (yrs.mths)	pathology/cause	side of insult	affected areas	age at time of investigation (yrs.mths)	time since insult (yrs.mths)
1 (SB)	9.4	infarct /vasculitis	right	sup/mid/inf frontal gyrus + sup/inf parietal lobe + putamen, head of caudate, internal capsule	22.0	12.8
2 (CJF)	7.7	infarct /haematological	left	sup/mid/inf frontal gyrus + putamen, head of caudate, insula, internal/external capsule	11.11	4.4
3 (SF)	4.4	infarct /dissection	left	mid/inf frontal + putamen, head of caudate, insula, internal/external capsule	13.0	8.8
4 (MC)	14.4	infarct /dissection	right	inf frontal, sup/mid temporal + sup/inf parietal + external capsule + putamen , caudate	14.10	0.6
5 (JM)	15.6	infarct/MCA dissection	right	putamen, head/body of caudate, insula, internal/external capsule	18.3	2.90
6 (AW)	3.5	infarct /undetermined	right	putamen, head of caudate, internal capsule	10.4	6.11
7 (AH)	15.0	infarct/ICA dissection	left	putamen, globus pallidus, head of caudate, internal/external capsule	17.2	2.2
8 (AK)	7.0	infarct/MCA stenosis	left	putamen, external capsule	14.4	7.3
9 (HC)	1.7	infarct /undetermined	left	putamen, body of caudate, internal capsule	12.11	11.4
10 (LB)	0.0	cortical dysplasia	left	temporal perisylvian + parietal region	8.10	8.10
11 (MT)	0.0	neuronal migration defect	right	temporal + parietal + occipital regions	16.2	16.2

Table 8.1: Summary of patients investigated. (sup=superior, mid=middle, inf=inferior, post=posterior).

8.3.1 Behavioural tests

The results of the sensory and motor behavioural tests are summarised in Table 8.2 and Table 8.3.

Patient	Side of damage	Handedness (score)	Tapping	Force production	Peg sorting	Finger opposition	Summary
1 (SB)	right	right (19)	L=70 R=74	L=18 R=20	L=11 R=9	Y	****
2 (CJF)	left	left	L=94 R=0	L=24 R=0	L=10 R=-	N	0
3 (SF)	left	left (68)	L=89 R=43	L=24 R=15	L=11 R=14	N	***
4 (MC)	right	right (19)	L=72 R=89	L=29 R=36	L=11 R=11	Y	****
5 (JM)	right	right (25)	L=0 R=89	L=6 R=48	L=- R=9	N	*
6 (AW)	right	right (18)	L=29 R=83	L=6 R=17	L=21 R=11	N	**
7 (AH)	left	ambidextrous (52)	L=87 R=67	L=37 R=37	L=12 R=13	Y	****
8 (AK)	left	ambidextrous (48)	L=88 R=42	L=22 R=17	L=10 R=12	N	***
9 (HC)	left	left (60)	L=86 R=35	L=18 R=7	L=9 R=23	N	**
10 (LB)	left	left	L=62 R=0	L=13 R=8	L=11 R=22	N	**
11 (MT)	right	right	L=24 R=50	L=13 R=42	L=73 R=16	N	**

Table 8.2: Motor tests. Units and abbreviations are as follows: tapping=number of finger taps per 20 seconds, force production=kg, peg sorting=seconds, R=right hand, L=left hand. For a description of the summary column refer to Section 8.2.1. Patients who showed a difference in motor function between the contra- and ipsilesional hand are shaded blue. - indicates those patients who were unable to complete the task.

Eight of the eleven patients who participated in the study had a clear motor deficit on the side of the body contralateral to that of the insult compared to the normal side at the time of the investigation. None of the eight patients was able to perform finger to thumb opposition in the hand contralateral to the affected hemisphere (refer to Table 8.2). Two of the eight patients had a mild motor deficit overall, four had a moderate motor deficit, one patient had a severe motor deficit and one patient had no motor function at all. Using the handedness inventory, it was shown that in nine patients the dominant hand was ipsilateral to the affected hemisphere. Five patients were reported to have changed their handedness as a result of the left-sided insult. Three patients showed a complete shift in handedness from right to left handed (patients 2, 3, and 9). The other two patients (one with no motor deficit and one with a mild motor deficit) were measured as being ambidextrous at the time of the investigation; both had previously been reported to be right handed (patients 7 and 8). No mirror movements were observed in any of the patients.

Patient	Side of damage	Double sim.stim. -hand	Position sense	Summary of residual function
1 (SB)	right	L=67 R=94	L=92 R=100	***
2 (CJF)	left	L=94 R=61	x	***
3 (SF)	left	L=100 R=60	x	***
4 (MC)	right	L=83 R=100	L=100 R=100	****
5 (JM)	right	L=72 R=100	L=75 R=100	***
6 (AW)	right	L=94 R=100	L=100 R=100	****
7 (AH)	left	L=89 R=100	L=100 R=100	****
8 (AK)	left	L=89 R=100	L=100 R=100	****
9 (HC)	left	L=100 R=100	x	****
10 (LB)	left	L=94 R=67	x	***
11 (MT)	right	L=89 R=100	x	****

Table 8.3: Sensory tests. Values listed in columns 3 and 4 represent percent of responses correct. (Double sim.stim.-hand=double simultaneous stimulation to the hand, R=right hand, L=left hand). For a description of the summary column refer to Section 8.2.1. Tests that were not performed in the patient are denoted x. Patients who showed a deficit in sensory function between the contra- and ipsilesional hand are shaded red.

The behavioural tests suggested that five patients had a mild sensory deficit in the hand contralateral to the side of the insult compared to the normal side (patients 1, 2, 3, 5, 10). None of the patients demonstrated a severe sensory deficit.

In summary, Table 8.2 and Table 8.3 collectively show that four patients had both motor and sensory deficits compared to their normal, ipsilesional side (patients 2, 3, 5, 10). In addition, four patients had only a motor deficit (patients 6, 8, 9, 11) and one patient had only a sensory deficit (patient 1). Only two patients did not show a motor or sensory deficit in the behavioural tests (patients 4 and 7). At the time of the initial insult, patient 7 was reported to have sustained a dense contralateral sensory and motor deficit, but this had completely recovered to normal by the time of the investigation.

8.3.2 SEP results

All of the 10 patients who underwent SEP investigations demonstrated contralateral responses following electrical and vibrational stimulation of the normal hand, which were similar to the control data presented in Chapter 6. The analysis of voltage maps of

individual components from these waveforms showed only contralateral peak responses, with no involvement of the ipsilateral hemisphere visible. Stimulation of the affected side (contralateral to the stroke) resulted in a number of different cortical responses in the patient group (see Table 8.4).

Patient	presence of normal c/l early latency components to electrical or vibration stimuli	c/l electrical components absent	c/l vibration components absent	presence of i/l response
1 (SB)	Y	long-latency (>50ms)		N
2 (CJF)	N	all	all	N
3 (SF)	Y			Y
4 (MC)	Y			N
5 (JM)	N		N70	N
6 (AW)	Y			N
7 (AH)	Y			N
8 (AK)	N		N70	N
9 (HC)	X			
10 (LB)	N		N70	Y
11 (MT)	N		all	N

Table 8.4: Summary of SEP findings following electrical and vibrational stimulation of the affected side in 11 patients. c/l=contralateral, i/l=ipsilateral, x=study not performed in this patient.

Five patients demonstrated abnormal early latency contralateral SEP responses following electrical or vibration stimuli; in one patient with frontal cortex and basal ganglia damage, the contralateral response following both electrical and vibrational stimulation was completely absent (patient 2), and in one patient with congenital disease encompassing the frontal and parietal lobes (patient 11) contralateral SEP responses were noted to be absent on vibrational stimulation only. The other three patients (patients 5, 8 and 10) showed no N70 component in response to vibration stimuli (for an example, see Figure 8.2). Two of these patients had basal ganglia and adjacent white matter infarcts and one had cortical dysplasia of the temporal and parietal regions.

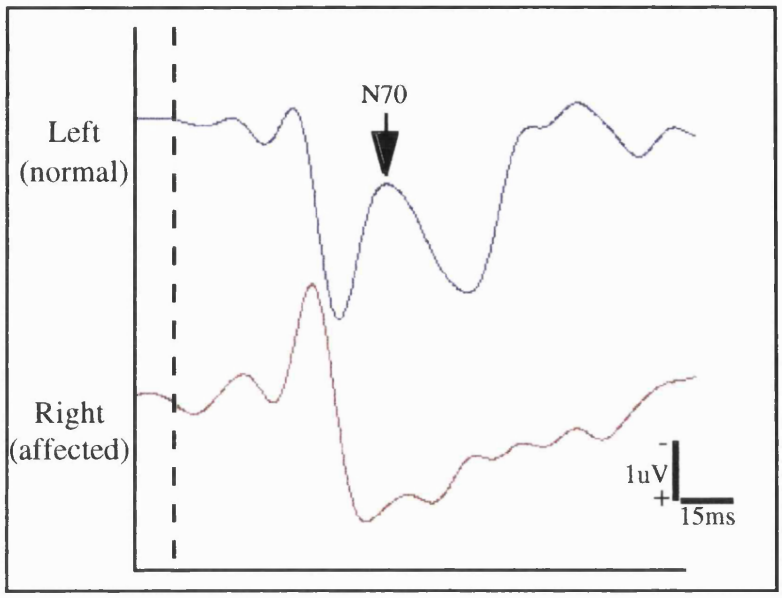


Figure 8.2: Patient 5. Contralateral SEP responses in the sensorimotor cortex following vibrational stimulation of the left (normal) and right (affected) index and middle finger. Arrow indicates the N70 component which is present in contralateral responses following stimulation of the normal hand, but absent in contralateral responses on stimulation of the affected hand.

Two patients (patients 3 and 10, the latter of whom also demonstrated no N70 component following vibration stimuli) showed early ipsilateral as well as contralateral SEP responses with stimulation of the affected side on topographical 2-D voltage maps. This bilateral response was recorded with vibration stimuli in patient 3 and electrical stimuli in patient 10. Figure 8.3 and Figure 8.4 show the contralateral and ipsilateral responses on stimulation of the affected and unaffected side in one electrode over the sensorimotor cortex for patients 3 and 10 respectively. These figures also show the corresponding voltage maps demonstrating the distribution of the response in each case at one particular time point of an early latency component. In each case, the ipsilateral component used for illustration and analysis was the most stable and recognisable. Patient 3 showed a bilateral response with vibration stimuli (Figure 8.3). The voltage maps show a contralateral and ipsilateral response on stimulation of the affected side, which are symmetrically distributed over the left and right hemispheres and spread over the superior aspect of the sensorimotor cortices and the vertex. Patient 10 demonstrated a bilateral response with electrical stimuli only (Figure 8.4). Voltage maps in this patient show an ipsilateral and contralateral response on stimulation of the affected side, represented symmetrically over the sensorimotor cortices of the left and right hemispheres. In both cases, the early latency ipsilateral response contained the same components as the comparable contralateral response following stimulation of the affected side.

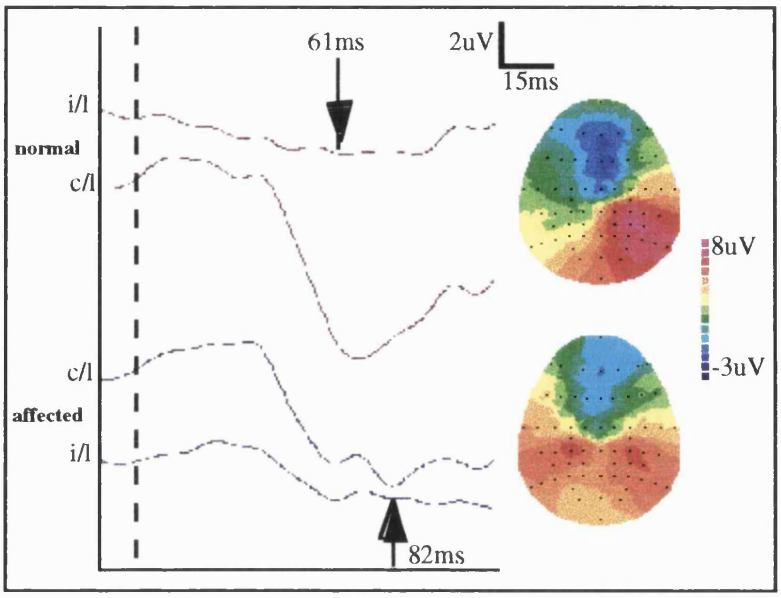


Figure 8.3: Patient 3: Comparative SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus on vibrational stimulation of the index and middle finger of the normal (left) and defective (right) side.

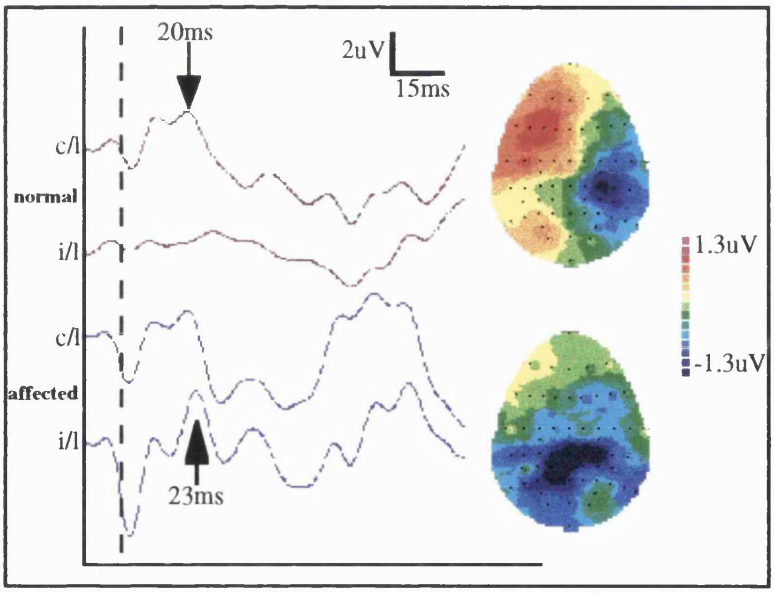


Figure 8.4: Patient 10: Comparative SEPs and topographical voltage maps recorded in symmetrical electrodes contralateral (c/l) and ipsilateral (i/l) to the stimulus on electrical stimulation of the median nerve of the normal (left) and defective (right) side.

One patient (patient 1) showed normal early latency SEP responses following vibration and electrical stimuli; however longer latency components (>50ms) were completely absent in response to electrical stimulation. This patient was distinct from all other patients in the study because she had suffered a stroke encompassing tissue in the parietal and frontal lobe, as well as in the basal ganglia. The parietal lobe is thought to be concerned with the detection and processing of both simple and complex sensory stimuli

(see Section 1.4.2 of Chapter 1), which could explain the abnormal contralateral SEP response.

The latency and amplitude of the earliest clear negative and positive latency SEP components were measured in each of the patients. These are labelled the N20/P30 for electrical stimulation and the N30/P60 for vibrational stimulation, as based on nomenclature from previous literature and data from this thesis (see Section 4.4.1 of Chapter 4). The results are shown in Table 8.5 and Table 8.6. In agreement with the findings of Chapter 4, the latency of SEP components in response to vibrational stimulation applied to the normal side was consistently longer than that of corresponding electrical SEP components. For electrical stimulation (Table 8.5), the contralateral SEP response on stimulation of the affected side was significantly smaller in amplitude compared to the unaffected side ($p<0.05$, paired t-test; mean±standard deviation=6.9±8.6 μV and 9.6±9.1 μV for stimulation of the affected and normal side respectively). Latency values for early components of stimulation of either side were not significantly different from each other (mean±standard deviation=24.0±5.4 ms and 24.8±6.2 ms for stimulation of the affected and normal side respectively). SEP findings following vibrational stimulation yielded similar results (Table 8.6). There was a significant decrease in the amplitude of the N30/P60 response in the affected compared to the unaffected side ($p<0.05$, paired t-test; mean±standard deviation=3.5±1.3 μV and 5.2±2.4 μV for stimulation of the affected and normal side respectively). As with electrical stimulation, there was no significant difference between the latencies of the early components in response to stimulation of either hand (mean±standard deviation=48.5±21.8 ms and 46.6±18.8 ms for stimulation of the affected and normal side respectively).

As stated previously, only two patients (patients 3 and 10) demonstrated ipsilateral SEP responses following stimulation of the affected hand. In both cases, the amplitude of the early ipsilateral SEP response was smaller and the latency of the early component was longer than the comparative contralateral response from stimulation of the affected side (see Table 8.5 and Table 8.6).

Patient	Stimulation of unaffected side		Stimulation of affected side			
	c/l latency N20/P30	c/l amplitude N20/P30	c/l latency N20/P30	c/l amplitude N20/P30	i/l latency N20/P30	i/l amplitude N20/P30
1 (SB)	18.8/29.1	6.4	20.7/30.8	2.8	NR	NR
2 (CJF)	19.9/28.6	22.1	NR	NR	NR	NR
3 (SF)	21.0/28.0	13.3	21.0/28.0	4	NR	NR
4 (MC)	19.8/34.9	7	19.3/35.9	2.8	NR	NR
5 (JM)	19.8/26.2	2.6	20.3/26.2	1.7	NR	NR
6 (AW)	18.9/29.6	32.1	16.4/28.1	28.5	NR	NR
7 (AH)	21.0/26.0	7	21.0/26.0	11.2	NR	NR
8 (AK)	20.8/33	10.4	18.4/26.2	5.2	NR	NR
9 (HC)	x	x	x	x	x	x
10 (LB)	20.8/38	2.1	21.3/30.7	2.5	23.4/31.6	1.9
11 (MT)	15.9/24.7	5.5	16.4/25.2	3.7	NR	NR

Table 8.5: Comparison of latency and amplitude measurements of the first early latency cortical components (N20 and P30) on electrical stimulation of the median nerve. (NR indicates no SEP response, x indicates study not performed).

Patient	Stimulation of unaffected side		Stimulation of affected side			
	c/l latency N30/P60	c/l amplitude N30/P60	c/l latency N30/P60	c/l amplitude N30/P60	i/l latency N30/P60	i/l amplitude N30/P60
1 (SB)	58.4/93.6	1.8	69.1/107.7	2	NR	NR
2 (CJF)	31.1/50.1	8.8	NR	NR	NR	NR
3 (SF)	32.5/62.8	7.6	30.6/55.5	5.1	31.5/56.0	2.2
4 (MC)	27.6/59.4	4.7	29.1/52.1	4.4	NR	NR
5 (JM)	44.7/57.4	3.1	50.1/64.3	3.5	NR	NR
6 (AW)	21.8/43.8	8.7	18.4/45.7	3.9	NR	NR
7 (AH)	27.0/60.0	4.8	28.0/60.0	4	NR	NR
8 (AK)	24.7/52.1	4.4	29.59/40.82	1.4	NR	NR
9 (HC)	x	x	x	x	x	x
10 (LB)	34.0/46.7	2.8	35.9/59.9	2.6	NR	NR
11 (MT)	34.0/57.9	3.6	NR	NR	NR	NR

Table 8.6: Comparison of latency and amplitude measurements of the first early latency cortical components (N30 and P60) on vibrational stimulation of the index and middle finger. (NR indicates no SEP response, x indicates study not performed).

8.3.2.1 Summary of SEP findings

Of the 10 patients who underwent SEP recordings, two patients did not show a response to electrical stimulation (patients 1 and 2) and vibrational stimulation (patients 2 and 11)

of the affected hand. A further three patients did not demonstrate an N70 component on vibrational stimulation of the affected hand (patients 5, 8, and 10). Ipsilateral as well as contralateral responses were observed in the voltage maps of two patients on stimulation of the affected hand; one with electrical and one with vibrational stimulation (patients 3 and 10).

8.3.3 fMRI results

Patients who had regained a significant degree of motor function following the insult in the contralesional hand, and who were co-operative enough to perform the task, carried out an active motor hand task (patients 1, 3, 4, 6, 7, 8, 9 and 10 from Table 8.1). Those patients who had difficulty in moving the contralesional hand underwent passive movement studies (patients 2, 5, and 11 in Table 8.1). The task performed by each of the eleven patients is shown in Table 8.7.

All of the patients who performed the tests demonstrated contralateral sensorimotor fMRI activation responses on movement of the normal hand, which were similar to the control data presented in Chapter 6. Three patients also demonstrated normal contralateral activation on movement of the affected hand, two had active movement and one hand passive movement (patients 4, 5, and 8; Table 8.7). Three of the patients did not show any activation on movement of the affected side, one had active movement and two had passive movement (patients 2, 6 and 11; Table 8.7). The other five patients demonstrated ipsilateral or bilateral fMRI activation on movement of the affected hand (patients 1, 3, 7, 9, and 10; Table 8.7). The findings in each of five patients with ipsilateral or bilateral activation are presented below. For each patient, the threshold for the display of activated regions is quoted as an uncorrected p-value. In addition, those regions which achieved significance when corrected for multiple comparisons are also indicated. Within an experiment, the relative significance of different regions of activation can be compared with yellow pixels being more significant than red; however, caution is required in comparing the significance of activation between experiments (for example between left and right hand movement studies) (see Section 3.5 of Chapter 3).

patient	motor task performed	isolated ipsilateral activation	bilateral activation	isolated contralateral activation
1 (SB)	active	-	Y	-
2 (CJF)	passive	-	-	-
3 (SF)	active	Y	-	-
4 (MC)	active	-	-	Y
5 (JM)	passive	-	-	Y
6 (AW)	active	-	-	-
7 (AH)	active	-	Y	-
8 (AK)	active	-	-	Y
9 (HC)	active	Y	-	-
10 (LB)	active	Y	-	-
11 (MT)	passive	-	-	-

Table 8.7: fMRI results: Column 2 shows the motor tasks that were performed by each of the patients. Columns 3, 4 and 5 report the fMRI results on movement of the affected (contralesional) hand.

8.3.3.1 Patient 1 (SB)

Patient 1 suffered a unilateral infarct in the right cerebral cortex and basal ganglia. The results are displayed at an uncorrected threshold of $p<0.01$, extent threshold of $p<0.05$ (Figure 8.5). Normal contralateral activation was visible on movement of the normal hand, which also reached significance when corrected ($P<0.001$). In contrast, bilateral activation was demonstrated on active movement of the impaired hand. The contralateral activation which also approached significance when corrected ($p=0.075$) appeared immediately anterior to the location of a visible lesion in the parietal lobe and extended anteriorly. It is difficult to locate the central sulcus in the right hemisphere in this patient; however, the location of the posterior border of the activated region lies in a sulcus which is consistent with the location of the central sulcus in the left hemisphere. The location of the ipsilateral activation overlapped partially with the region activated on movement of the contralateral hand, but also appears to extend anteriorly along a sulcus by approximately 1-2 cm, a region not visibly activated by the normal contralateral hand. The ipsilateral region of activation also reached a corrected level of significance ($P<0.001$). The ipsilateral activation is smaller in extent overall than the contralateral activation that is observed on movement of the normal hand. Interestingly, the location of the supplementary motor area activation is very similar on movement of the left and right hand (on the medial border of the left hemisphere). The supplementary motor area activation also reached significance when corrected with movement of both the left and right hand ($p<0.01$).

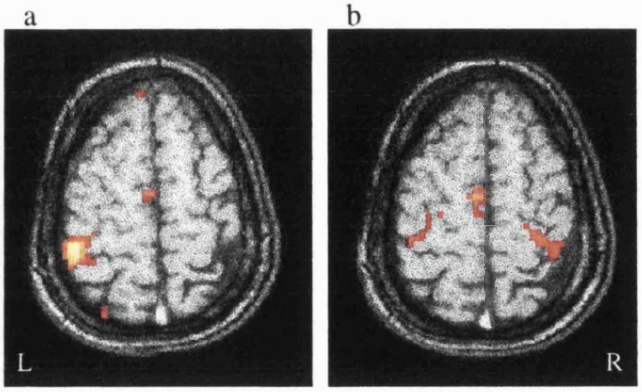


Figure 8.5: Patient 1. fMRI activation maps on normal (a) and affected (b) hand active movement studies in a single axial slice. See text for description.

8.3.3.2 Patient 3 (SF)

Patient 3 had a left cortical and subcortical infarct. In this patient, fMRI studies were repeated in two separate sessions. The results for the two sessions are displayed at an uncorrected significance level of $p<0.01$ for movement of the normal hand and $p<0.2$ for movement of the affected hand (extent threshold $p<0.05$). The fMRI findings from two separate sessions showed contralateral activation on active movement of the normal hand (in both sessions these contralateral regions also reached corrected significance ($p<0.001$)). Only ipsilateral activation was seen on active movement of the impaired hand (Figure 8.6). In the first session this ipsilateral activation approached uncorrected significance ($p=0.079$); in the second session the ipsilateral activation, although not significant, was located in a very similar region to that activated in the first session. In both cases, the region of ipsilateral activation was small in spatial extent, but still reached significance at $p<0.05$. The location of the ipsilateral activation was similar to a subregion of the activation seen on movement of the normal hand. The peak ipsilateral activation was slightly different in location between the two sessions; in session 2 the peak activation was located in a slice 6 mm below that seen in session 1.

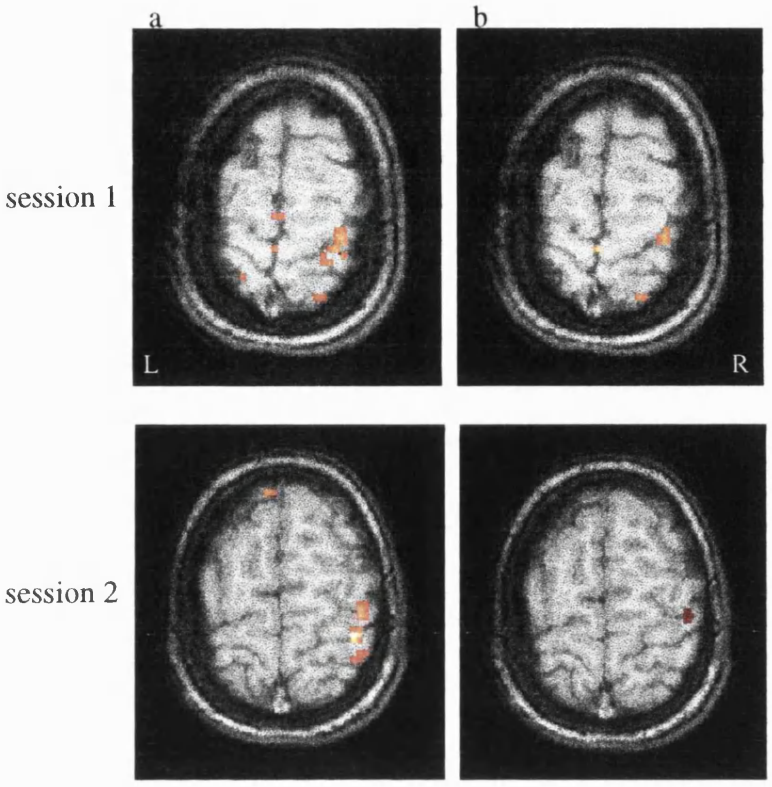


Figure 8.6: Patient 3. fMRI activation maps on active movement of the normal (a) and defective hand (b) in one axial slice. The experiment was repeated in two separate sessions, labelled 1 and 2.

8.3.3.3 Patient 7 (AH)

Patient 7 had an infarct within the left basal ganglia and adjacent white matter. The activation images are displayed at an uncorrected significance threshold of $p<0.01$, extent threshold $p<0.05$ (Figure 8.7). fMRI findings showed contralateral activation on active movement of the normal (left) hand which reached corrected significance ($p<0.001$). Bilateral activation, however, was seen on active movement of the affected (right) hand. The activation seen in the left (contralateral) hemisphere on right hand movement also approached corrected significance ($p=0.076$). The location and spatial extent of ipsilateral activation was similar to that seen on movement of the normal contralateral hand. The contralateral signal change lying on the lateral edge of the central sulcus may be a result of a draining blood vessel.

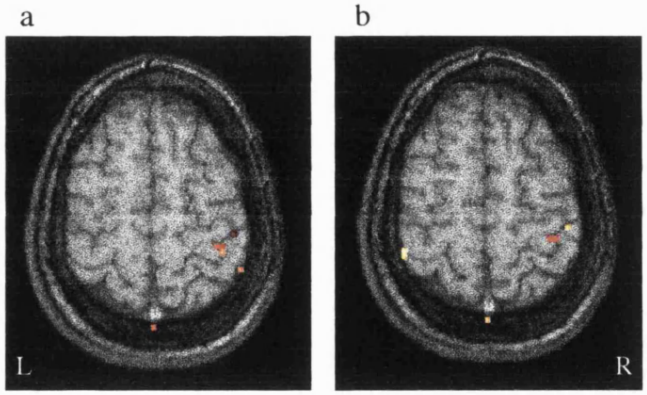


Figure 8.7: Patient 7. fMRI activation maps for active movement of the normal (a) and defective (b) hand in one axial slice.

8.3.3.4 Patient 9 (HC)

Patient 9 had an insult damaging the left basal ganglia and adjacent white matter. The fMRI results in this patient are displayed at an uncorrected p-value threshold of $p<0.05$, extent threshold $p<0.05$. fMRI showed contralateral activation on active movement of the normal (left) hand, but only ipsilateral activation on active movement of the impaired (right) hand (Figure 8.8). Only the activation for movement of the normal hand reached corrected significance ($p<0.001$). The ipsilateral activation was similar in location but smaller in extent compared to that seen on movement of the normal hand.

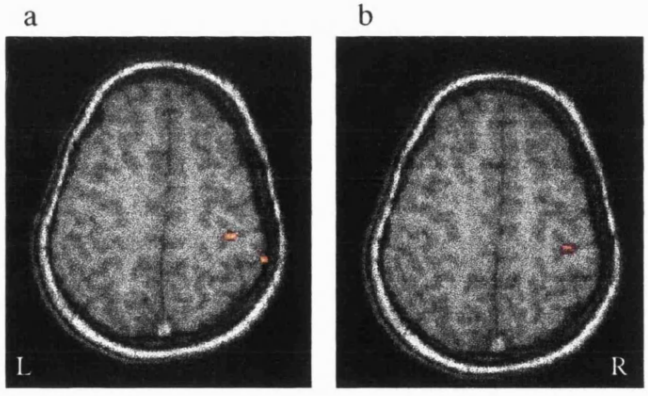


Figure 8.8: Patient 9. fMRI activation maps for active movement of the normal (a) and defective (b) hand in a single axial slice.

8.3.3.5 Patient 10 (LB)

Patient 10 had a congenital cortical dysplasia affecting the temporal and parietal lobes of the left hemisphere. In this patient, fMRI studies were repeated in two separate sessions. The fMRI results are displayed at an uncorrected significant p-value threshold of $p<0.05$ for session 1 and $p<0.01$ for session 2 (extent threshold $p<0.05$) (Figure 8.9). The results showed contralateral activation on active movement of the normal hand, but only ipsilateral activation on active movement of the defective hand. In both sessions these contralateral and ipsilateral regions of activation also reached corrected significance ($p<0.05$). In session two, a small region of ipsilateral activation on active movement of the normal hand was also observed in the affected (left) hemisphere, but this region did not reach corrected significance (Figure 8.9). The location of the ipsilateral activation with movement of the affected hand was similar to that seen contralaterally on movement of the normal side. In both studies, the spatial extent of the ipsilateral activation was smaller than that of the normal contralateral activation.

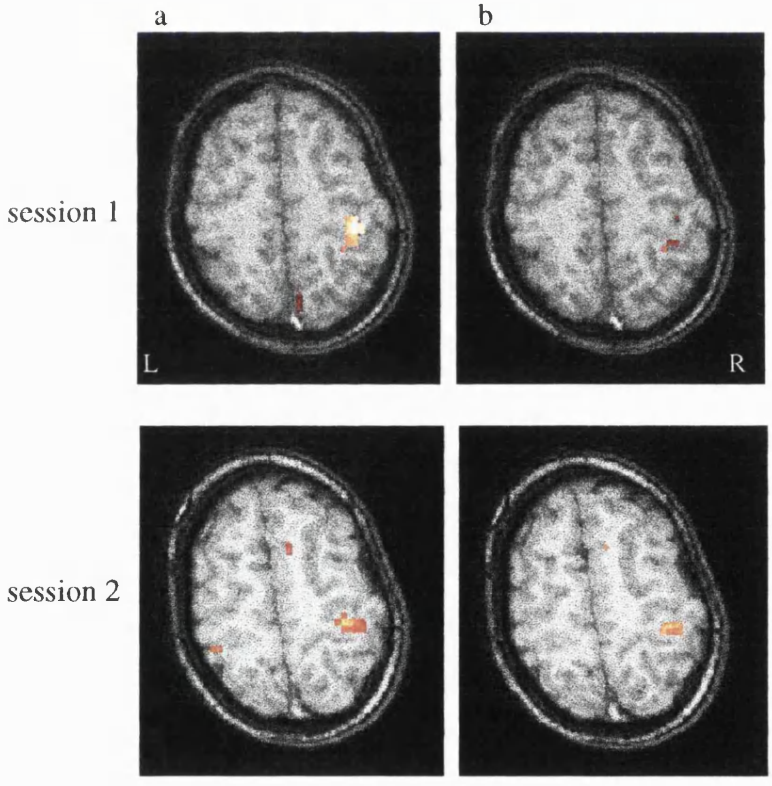


Figure 8.9: Patient 10. fMRI activation maps for active movement of the normal (a) and defective (b) hand in a single axial slice. The experiment was repeated in two separate sessions, labelled 1 and 2.

8.3.3.6 Summary of fMRI findings

A summary of the fMRI results in this group of patients is given in Table 8.7. Three patients demonstrated only ipsilateral sensorimotor cortex activation with movement of the impaired hand (patients 3, 9, and 10). All of these patients had performed an active movement task. In all three cases, the ipsilateral activation seen on fMRI appeared to be similar in location to the region of cortical activation observed on movement of the normal side. In two of these patients in whom fMRI was performed in two separate sessions, the ipsilateral activation was shown to be reproducible (patients 3 and 10). In all cases, the region of ipsilateral activation appeared smaller in spatial extent than the region of contralateral activation seen on movement of the normal side. Two patients (patients 1 and 7) showed bilateral activation on active movement of the defective hand. In patient 7, the ipsilateral activation on movement of the affected hand was similar in location to the contralateral activation on movement of the normal hand. In patient 1, in addition to contralateral activation, movement of the affected side produced ipsilateral activation in two adjoining regions; one that was located in a region similar to that activated on movement of the normal side, and a second region that extended anteriorly in the frontal lobe.

8.3.4 Overall summary of patient results

A summary of the findings from the behavioural tests, fMRI and SEP investigations (see Sections 8.3.1, 8.3.3 and 8.3.2) is given in Table 8.8.

Patient	Motor function	Sensory function	Shift in handedness	Contralateral fMRI activation	Ipsilateral fMRI activation	Contralateral SEP responses	Ipsilateral SEP response
1 (SB)	* * * *	* * *	N	Y	Y (bi)	Y	N
2 (CJF)	0	* * *	Y	N	N	N	N
3 (SF)	* * *	* * *	Y	N	Y (ip)	Y	Y
4 (MC)	* * * *	* * * *	N	Y	N	Y	N
5 (JM)	*	* * *	N	Y	N	Y	N
6 (AW)	* *	* * * *	N	N	N	Y	N
7 (AH)	* * * *	* * * *	Y	Y	Y (bi)	Y	N
8 (AK)	* * *	* * * *	Y	Y	N	Y	N
9 (HC)	* *	* * * *	Y	N	Y (ip)	X	X
10 (LB)	* *	* * *	N	N	Y (ip)	Y	Y
11 (MT)	* *	* * * *	N	N	N	Y (electrical)	N

Table 8.8: Summary of behavioural, fMRI and SEP findings. X indicates that the study was not performed, the number of * indicates the degree of residual sensory or motor function contralateral to the lesioned side (refer to Section 8.2.1 for categorisations). Contralateral and ipsilateral fMRI results are summarised as Y (yes) and N (no); (ip) = ipsilateral, (bi) = bilateral. The results of the SEPs are reported as a response to either electrical and/or vibrational stimulation (electrical = contralateral response seen on electrical stimulation only). Patients demonstrating ipsilateral or bilateral fMRI and SEP responses are shaded red, patients showing ipsilateral fMRI responses only are shaded blue.

In order to more easily compare the fMRI and SEP data with residual motor function and age at injury, the data were re-tabulated (Table 8.9 and Table 8.10, respectively).

Patient	Congenital/ acquired damage	Residual motor function	ipsilateral fMRI	ipsilateral SEPs
1 (SB)	acquired	* * * *	Y (bil)	N
7 (AH)	acquired	* * * *	Y (bil)	N
3 (SF)	acquired	* * *	Y (unilat)	Y
10 (LB)	congenital	* *	Y (unilat)	Y
9 (HC)	acquired	* *	Y (unilat)	X
4 (MC)	acquired	* * * *	N	N
6 (AW)	acquired	* *	N	N
8 (AK)	acquired	* * *	N	N
5 (JM)	acquired	*	N (passive)	N
11 (MT)	congenital	* *	N (passive)	N
2 (CJF)	acquired	0	N (passive)	N

Table 8.9: Summary of ipsilateral fMRI and SEP findings with residual motor function (bil=bilateral primary sensorimotor cortex, unilat=unilateral ipsilateral primary sensorimotor cortex). (passive) indicates patients who performed a passive hand motor task. For a description of the grading for residual motor function refer to Section 8.2.1.

Subject	sex	handedess	right hand movement	left hand movement
1	male	right	c/l	c/l
2	male	right	c/l	c/l
3	female	right	c/l	c/l
4	female	right	c/l + i/l	c/l + i/l
5	female	right	c/l + i/l	c/l + i/l
6	female	right	c/l	c/l
7	male	left	c/l + i/l	c/l + i/l
8	male	left	c/l + i/l	c/l
9	female	left	c/l + i/l	c/l + i/l
10	female	left	c/l	c/l

Summary of contralateral (c/l) and ipsilateral (i/l) sensorimotor cortex fMRI activation following active movement of the left and right hand in 10 adult volunteers of left and right handedness. This Table and Table 8.10 are compared in Section 10.2 (page 247).

Patient	age at injury (yrs.mnths)	ipsilateral fMRI	ipsilateral SEPs
10 (LB)	0.0	Y (unilat)	Y
11 (MT)	0.0	N	N
9 (HC)	1.7	Y (unilat)	X
6 (AW)	3.5	N	N
3 (SF)	4.4	Y (unilat)	Y
8 (AK)	7.0	N	N
2 (CJF)	7.7	N (passive)	N
1 (SB)	9.4	Y (bil)	N
4 (MC)	14.4	N (passive)	N
7 (AH)	15.0	Y (bil)	N
5 (JM)	15.6	N (passive)	N

Table 8.10: Summary of ipsilateral fMRI and SEP findings compared with the age at injury (bil=bilateral primary sensorimotor cortex, unilat=unilateral ipsilateral primary sensorimotor cortex). (passive) indicates patients who performed a passive hand motor task.

Of the patients who carried out SEP recordings, both of the patients who demonstrated ipsilateral SEPs, also demonstrated ipsilateral fMRI activation. Statistical analysis of the data in the 11 patients showed that there was no significant association between the incidence of ipsilateral electrical SEP responses and the extent of residual motor and sensory function on tapping (p=69; Wilcoxon-Mann-Whitney Test), peg sorting (p=0.9; Wilcoxon-Mann-Whitney Test), dynamometer (p=1.0; Wilcoxon-Mann-Whitney Test), and double simultaneous stimulation (p=0.12, Wilcoxon-Mann-Whitney Test). There was also no significant association between the presence of ipsilateral fMRI activation and the extent of residual motor and sensory function on tapping (p=0.61; Wilcoxon-Mann-Whitney Test), peg sorting (p=0.76; Wilcoxon-Mann-Whitney Test), dynamometer (p=1.000; Wilcoxon-Mann-Whitney Test) and double simultaneous stimulation (p=0.41, Wilcoxon-Mann-Whitney Test). There was no significant relationship between the age of brain damage and the presence of either ipsilateral electrical SEP responses (p=0.19, Wilcoxon-Mann-Whitney Test), or ipsilateral fMRI activation (p=0.1, Wilcoxon-Mann-Whitney Test). There was also no statistically significant association between the site of brain damage (cortical/subcortical or subcortical) and the presence of ipsilateral electrical SEP responses (p=0.467, Fishers Exact Test)) or the presence of ipsilateral fMRI activation (p=1.000, Fishers Exact Test).

As reported in Section 8.3.1, five of the 11 patients reported a change in handedness after the brain insult. Statistical analysis showed that there was no significant association between this change and the presence of ipsilateral fMRI activation (p=0.545, Fishers Exact Test) or the presence of ipsilateral SEPs (p=1.000, Fishers Exact Test). There was, however, a statistically significant association between the patient's handedness (at

the time of testing) and the presence of ipsilateral fMRI activation (p=0.048, Fishers Exact Test). Statistical analysis between ipsilateral SEPs and the patient's handedness at the time of testing also approached significance (p=0.089, Fishers Exact Test).

8.4 Discussion

In this study, the cortical substrate subserving residual sensorimotor function in children with infarcts or congenital brain damage has been investigated using fMRI and SEP. The following discussion concentrates on the findings in this study in patients with brain infarcts. However, many of the issues are re-addressed in the General Discussion (Chapter 10), in conjunction with findings from hemispherectomy patients (Chapter 7) and patients with discrete brain lesions (Chapter 9).

8.4.1 Reorganisation of sensorimotor function

A number of patients in the present study demonstrated apparent reorganisation of sensorimotor function, revealed as the recruitment of the ipsilateral sensorimotor cortex. Involvement of the ipsilateral sensorimotor cortex was seen more readily using fMRI (5 out of 11 patients; 3 with isolated ipsilateral fMRI activation) than SEP recordings (2 out of 11 patients showed bilateral SEPs). This difference between the results of the two techniques may reflect differences in the sensitivity for the detection of a response that is specific to this patient population (this difference, however, is opposite to that found in hemispherectomy patients reported in Chapter 7, and will be discussed in Chapter 10).

The fMRI study in control subjects reported in Chapter 6 demonstrated that active and passive movement tasks resulted in activation in the contralateral primary sensorimotor cortex in all cases studied. The peak responses from both tasks were similar in location. Moreover, in several volunteers of mixed handedness, active movement produced both contralateral and ipsilateral primary sensorimotor cortex fMRI activation; however in all cases only contralateral activation was present on passive movement. In the present study, patients performed either active or passive movement tasks, depending on their residual motor ability in the affected hand. Three patients demonstrated isolated ipsilateral activation following active movement of the affected hand. This is suggestive of a disruption or reorganisation of the entire motor system by a unilateral focal lesion (as suggested previously, for example Dettmers et al. 1997; Weder & Seitz, 1994). It appears that in some patients recovering from hemiparesis after unilateral stroke, functional motor pathways may reorganise in an attempt to recruit any pre-stroke link

between the paretic hand and the primary motor cortex in the non-infarcted hemisphere (for a review of the SEP and fMRI literature refer to Section 8.1.3, and also PET and TMS studies for example Turton et al. 1996; Netz et al. 1997; Chollet et al. 1991; Honda et al. 1997). In the absence of contralateral activation in the lesioned hemisphere, it appears that the ipsilateral activation is demonstrating the recruitment of the ipsilateral sensorimotor cortex in the recovery of hand function, and hence inter-hemispheric reorganisation of sensorimotor function. The presence of ipsilateral activation in patients recovering from stroke is in agreement with a number of previous fMRI studies (Cramer et al. 1997; Cao et al. 1998). In particular, Cao et al. (1998) reported that three of the eight stroke patients in their study demonstrated ipsilateral activation alone. All three patients suffered infarctions in the postcentral gyrus, in contrast with the cortical and subcortical lesions seen in the patients in the present study. In addition, one recent study in a 13 year old patient with extensive unilateral cortical dysplasia demonstrated ipsilateral SEP responses in the unaffected hemisphere following stimulation of the paretic side, with the absence of contralateral responses (Maegaki et al. 1995). The one patient who had cortical dysplasia in this study demonstrated ipsilateral fMRI activation and bilateral SEP responses. This is consistent with the findings of Maegaki et al. (1995) showing that patients with such congenital malformations may also exhibit inter-hemispheric reorganisation through activity in the contralesional hemisphere.

Two patients in the present study demonstrated bilateral fMRI activation with active movement of the affected hand in the primary sensorimotor cortices. It is not clear whether this bilateral primary sensorimotor cortex activation is a normal phenomenon in these patients (as in control studies, see Section 6.3.1.1.2 of Chapter 6) or results from reorganisation of the sensorimotor systems. None of the patients in this study had mirror movements. The results of these two patients are similar to those found by Cramer et al. (1997). They reported that ipsilateral activation was only present in addition to contralateral activation in the affected hemisphere during an active finger tapping task.

Although some studies have reported homotopic inter-hemispheric reorganisation into primary sensorimotor cortex of the undamaged hemisphere as described above, other studies suggest predominantly non-homotopic reorganisation (i.e. reallocation of motor functions into secondary motor regions or regions that are not primarily dedicated to motor function in the normal brain) (for example Weiller et al. 1992; Seitz et al. 1998). Several of these studies have shown non-homotopic activation predominantly in the ipsilateral hemisphere to the paretic hand, for example in the ipsilateral premotor cortex, SMA, and parietal cortex (Cao et al. 1998; Weder et al. 1994; Honda et al. 1997; Dettmers et al. 1997). In the present study, one patient (patient 1), who had a mild

sensory deficit and normal motor function, demonstrated ipsilateral activation that was located in both the primary sensorimotor cortex (similar to contralateral activation on movement of the normal side) and an additional area which extended anteriorly in the frontal lobe. Due to the abnormal anatomical features of the sulci in this patient (see Figure 8.5), it is difficult to draw a firm conclusion as to the functional area subserving the ipsilateral activation anterior to the primary motor cortex. It is likely, however, that this anterior ipsilateral activation could be in the premotor cortex (see Section 1.3.2 of Chapter 1 for a brief description of this area), reflecting both inter- and intra-hemispheric reorganisation (further discussed in Chapter 10).

8.4.2 Factors influencing functional recovery and brain reorganisation following infarction

A number of investigations have been carried out attempting to relate the presence of ipsilateral cortical sensorimotor responses to the sensory and/or motor functional outcome in patients following damage to the sensorimotor area of one hemisphere (such as Fries et al. 1991; Turton et al. 1996). In the present study there was no significant association between the presence of ipsilateral responses using fMRI or SEPs and residual sensory or motor functional outcome in the affected hand of the patient (see also Table 8.9). Several recent TMS studies found that the motor outputs in the unaffected ipsilateral hemisphere may be significantly changed following stroke, but that the existence of these responses was not correlated with clinical improvement (Turton et al. 1996; Netz et al. 1997). In fact, ipsilateral responses from the intact side were more prevalent in patients who had only partial recovery and a remaining paresis after stroke; the patients with good recovery did not differ from normal control subjects. This has also been supported by fMRI studies, reporting ipsilateral precentral gyrus activation in patients with a motor deficit following stroke (Presciutti et al. 1996, 1998). A correlation has, however, been demonstrated by several other studies between improved residual function and the presence of ipsilateral sensorimotor responses. Studies using PET imaging have suggested that ipsilateral motor centres and pathways may play a role in motor recovery (for example Chollet et al. 1991; Weiller et al. 1992). A transcranial Doppler study in patients with cortical ischaemic stroke showed a greater increase in the flow velocity of the ipsilateral middle cerebral artery during movements of the recovered hand compared to movement of the unaffected hand and control subjects, which may be related to the recovery of motor function (Silvestrini et al. 1995, 1998). Caramia et al. (1996) also reported that in patients with rapid motor functional recovery after stroke, transcranial stimulation of either the lesioned or normal hemisphere always elicited ipsilateral MEPs during voluntary contraction. This present study has not shown any

evidence for the recruitment of the ipsilateral sensorimotor cortex in subserving sensorimotor recovery following infarcts to the brain. It is clear from the literature that more studies are needed to determine the involvement of the ipsilateral sensorimotor cortex in functional recovery.

In this study, five patients changed handedness as a result of the stroke (patients 2, 3, 7, 8, and 9). As reviewed in Section 5.2.2.5 of Chapter 5, a change in handedness has been shown previously to be dependent on the side of the brain that is damaged and on the patient's handedness before the insult (for example Isaacs et al. 1996). In particular, studies have shown that early left hemisphere injury frequently leads to an increased rate of left-handedness (for example Vargha-Khadem et al. 1985). This is consistent with the fact that the majority of people are naturally right-handed (Ellis et al. 1988), and after left-sided brain damage may show an increased rate of left-handedness due to a shift in handedness, compared to the relatively small number of pathological right-handers that may occur after right hemisphere insults. Concordant with this finding, all five patients in the present study who showed a change in handedness as a result of the stroke had suffered left hemisphere damage affecting either cortical and/or subcortical tissue. All of these patients were initially right-handed before the stroke occurred. Of these five patients, two demonstrated isolated ipsilateral fMRI activation, one of whom demonstrated bilateral SEP responses with the affected hand (patients 3 and 9). A further patient (patient 10) who showed ipsilateral fMRI and bilateral SEP responses did not show a change in handedness as a result of the left-hemisphere stroke, but this patient was left-handed before the stroke occurred. Statistical analysis showed a significant association between the patients' handedness and the presence of ipsilateral fMRI activation (the p-value also approached significance for handedness versus ipsilateral SEP response). However, there was no significant association between a change in the patients' handedness and the detection of ipsilateral responses (the data of patient 10 showing no change in handedness may influence this non-significant result). However, due to only a small number of patients, it is difficult to draw any conclusions from these findings.

There was no significant association in the present study between ipsilateral responses on fMRI or SEPs and the age of injury (see Table 8.10). In addition, there was also no significant association between the demonstration of ipsilateral fMRI and SEP responses (patients 1, 3, 7, 9, and 10) and the location of damage in this group of patients (cortical/subcortical or subcortical). Of the five patients who demonstrated ipsilateral responses, two had an infarct affecting both cortical and subcortical regions, two had suffered an infarct in the basal ganglia (and adjacent white matter), and one patient had

cortical dysplasia of the temporal and parietal lobes (refer to Table 8.1). There also appears to be no relationship between the side of damage and the presence of ipsilateral responses (of the five patients with ipsilateral responses, four patients had left hemisphere damage and one had damage to the right hemisphere). Also, the age at the time of the investigation since the brain insult (from 2.2 to 12.8 years.months; mean age 8 years 7 months) varied considerably between the patients who demonstrated ipsilateral responses. This is in agreement with previous studies showing considerable individual variation in the patterns of activation of both the ipsilateral and contralateral hemispheres following recovery from hemiparesis (see Section 8.1.3).

In the present study, the location of the infarct (either cortical or subcortical) or the timing of the lesion (congenital or acquired) appeared not to be related to the degree of sensory or motor functional recovery (compare Table 8.1 and Table 8.8). The findings in this study appear to be in agreement with those reported by Bonita & Beaglehole (1988) and Pantano et al. (1996), who did not demonstrate a relationship between residual sensory or motor function and the location or side of the lesion or the age or gender of the patient. In addition, no obvious relationship was found between the residual sensorimotor function and the time between investigation and the stroke, in contrast with the findings of Pantano et al. (1996) who suggested that the eventual degree of motor function negatively correlated with the time from the stroke until entry into the study. Our data also suggest that a large proportion of patients may not fully recover sensory or motor function in their upper limb following infarcts or congenital damage. In this study, a high proportion of patients were reported to remain with a deficit in the upper limb and hand; 9 out of 11 patients had a motor deficit (2 patients having very little function and one patient had no motor function) and of these patients four also had a mild sensory deficit. In addition, one patient was reported to have a mild sensory deficit only. Only one patient (who had suffered a subcortical stroke) did not have a sensory or motor deficit at the time of the investigation. In general, the literature has reported contradictory findings regarding the extent of residual sensory or motor outcome following stroke (Section 8.1.3.3). Gresham et al. (1979) reported in a group of stroke patients that only a small percentage of patients are left with no, or minimal, disability. Similarly, Duncan et al. (1992) showed that most patients had severe and persistent motor deficits which affected their daily activities in varying degrees. In contrast, out of a population of 148 long-term survivors of stroke, persistent hemiparesis and hemisensory defects have been reported in a much smaller proportion of patients (45% and 36% respectively) (Gresham, 1986). Clearly, more research with a greater number of patients is needed to establish the likely residual sensorimotor function

for a patient following an infarct in the brain, and also to identify the factors that may influence functional outcome (further discussed in Chapter 10).

8.4.3 Specific issues pertinent to the SEP results

This is the first study to demonstrate ipsilateral as well as contralateral SEP responses in patients recovering from stroke (refer to Section 8.1.3.1). The ipsilateral response in both cases was smaller in amplitude and longer in latency compared to the counterpart contralateral response. In addition, the contralateral SEP responses following stimulation of the affected hand had a significantly decreased amplitude compared with stimulation of the unaffected hand, a finding that has been extensively reported in stroke patients previously (for example Williamson et al. 1970; Regli & Despland, 1982; Stejskal & Sobota, 1985; refer to Section 8.1.3.1). However, inconsistent with previous studies, there was no observed increase in latency in SEP components on stimulation of the affected compared to the unaffected side.

In this study, two of the patients demonstrated both ipsilateral and contralateral SEP responses with stimulation of the affected hand. A surprising finding, however, was the inconsistency of the bilateral SEP responses with the stimulus applied. Although each patient had both investigations, bilateral responses were demonstrated only following vibration stimuli in one patient, and with electrical stimulation in the other. Chapter 4 reports normative data for cortical SEPs with electrical and vibration stimuli. Contralateral electrical and vibrational SEPs are reported in Chapter 4 that were found to contain comparable components between the two stimuli; however responses were smaller in amplitude and longer in latency for vibration than for electrical stimuli (also supported by Hamalainen et al. 1990). These differences between the SEP responses of the two stimuli types may reflect differences in the fibre pathways activated, or in their number and degree of synchronicity (less synchronous stimulation of fibres seen with vibration) resulting from the stimuli used. This would suggest that vibrational SEPs would be less effective in demonstrating subtle changes in the sensorimotor system following brain damage than electrical stimulation. It is also possible that, given the small number of patients who demonstrated bilateral responses, the inconsistency could be due to individual differences or simply be a chance occurrence. Despite these considerations, there still appears to be no clear explanation for the difference in ipsilateral responses recorded with different stimuli in two patients in this study.

There has been controversy as to whether a correlation exists between the location of the stroke and the absence of early latency SEP components (Yamamoto et al. 1995). As

none of the patients in this study had suffered cortical strokes affecting only the pre- or postcentral gyrus, it is not possible to compare these findings with other reports of focal strokes in such areas (see Section 8.1.3.1). This study has, however, shown an absence of the N70 component of the vibrational SEP in three patients with stimulation applied to the affected hand (this loss was also seen in separate runs in the same patient). However, the location and timing of the insult to the brain was different in all three patients; either acquired basal ganglia (and adjacent white matter) lesions or congenital cortical lesions (compare Table 8.1 and Table 8.4). The N70 component is thought to be generated in the primary sensory cortex, but studies also suggest that there may also be a contribution from the secondary somatosensory cortex (Hamalainen et al. 1990). As there is very little literature demonstrating the detailed role and location of this component, it is unclear why only this component appears to be affected by the variable brain lesions in these patients.

A final point to note concerns two patients who did not show any SEPs following vibrational stimulation of the affected hand. One of these patients also failed to show cortical activity following electrical stimulation of the same hand. Both of these patients, however, had mild or normal sensory function at the time of testing (compare Table 8.4 and Table 8.3). It is possible that the primary sensory cortex is still intact, but reduced in activity to a level that is not detected using SEP measures of cortical function.

8.5 Conclusions

This study has demonstrated that inter- and intra-hemispheric reorganisation of the sensorimotor system can occur in patients with brain infarcts. Isolated ipsilateral responses were seen in 3 out of 11 patients using fMRI with active movement of the affected hand, and bilateral responses seen in 2 out of 11 patients using SEP recordings following stimulation of the affected hand. No relationship was found between the presence of ipsilateral fMRI or SEP responses and the degree of residual motor function, the age at injury, or the location of damage (this was also found in hemispherectomised patients reported in Chapter 7, and will be further discussed in Chapter 10).

Chapter 9: Pre-surgical fMRI investigations in children with intractable epilepsy

9.1 Introduction

Children with intractable epilepsy may undergo surgery for relief from seizures (Thuxhorn et al. 1997). In many cases, such surgery may need to be carried out within or adjacent to eloquent cortex. One of the issues addressed in neurosurgical planning is the anatomical relationship between the location of functionally eloquent cortex and the cortical area targeted for surgical resection. The primary functional areas critical for neurosurgical planning are those related to sensory, motor, speech, language and memory function. Accurate localisation of these functional brain areas is essential to minimise post-operative neurological deficits in patients where the lesion to be resected lies in or adjacent to the site of eloquent cortex. An obvious potential application of fMRI, therefore, is in presurgical planning. The first reported study of fMRI mapping of the sensory and motor cortex for surgical planning was performed by Jack et al. (1994). A number of studies have since confirmed the value of fMRI in the localisation of functionally eloquent cerebral cortex, including motor, sensory, language and visual areas (for example Latchaw & Hu, 1995; Puce, 1995; Puce et al. 1995; Stapleton et al. 1997; Yetkin et al. 1997).

In many cases, the sensorimotor cortex can be identified prior to surgery using anatomical landmarks. However, normal sulcal anatomy may be considerably distorted by a space-occupying lesion or oedema. In addition, there may be potential movement of tissues during the operation as a direct result of the craniotomy. This would affect the applicability of the pre-surgical localisation procedures, such as fMRI, to the brain intra-operatively. As a result, cortical stimulation continues to be applied intra-operatively to locate the functional areas of the brain such as the motor and sensory cortex and language areas (Black & Ronner, 1987; Ebeling & Reulen, 1995). In the majority of fMRI studies, the findings have correlated with such intraoperative cortical stimulation (such as Yousry et al. 1995).

A second invasive method of functional cortical brain mapping is by means of the implantation of subdural electrodes. Electrode grids positioned over the sensorimotor cortex permit both the accurate localisation of an epileptogenic focus in the cortex and

also the mapping of surrounding eloquent functional areas. Since the pioneering work performed by Woolsey et al. (1949), there have been numerous reports of direct cortical recordings of SEPs in the human cortex to identify and map the sensory cortex (among others, Allison et al. 1989a; Puce et al. 1995; Wood et al. 1988; Cakmur et al. 1997). In addition, stimulation via the subdural grid provides a method for mapping the sensory and motor cortex, using a similar principle to that of intra-operative cortical stimulation (for example Uematsu et al. 1992a; Jack et al. 1994; Detre et al. 1995).

9.1.1 Aims of this study

The aims of this study were three-fold:

- To localise the hand primary sensorimotor area using fMRI in a group of children prior to the neurosurgical resection of brain lesions in the vicinity of the primary sensorimotor cortical areas.
- Where possible, to compare the fMRI finding to the location of the hand sensorimotor area obtained using intra-operative cortical stimulation or invasive monitoring with subdural electrodes.
- To look for possible changes in the cortical sensory or motor representation induced by the presence of a lesion or damaged tissue in the vicinity of the primary sensorimotor area.

9.2 Methods

Studies were carried out in twelve children with intractable epilepsy (4 females and 8 males) who were being worked up for neurosurgery. Their ages ranged from 9 to 17 years (mean 14 years). As with the control subjects described in Chapter 6, all patients had fMRI investigations of both left and right hand movement. Patients were selected on the basis that they were likely to be able to co-operate during the fMRI examination and that they did not require sedation.

9.2.1 fMRI

The protocol used for the fMRI data acquisition is described in detail in Section 3.4 of Chapter 3. Images were displayed at an uncorrected p-value threshold of $p<0.01$, extent

threshold $p<0.05$. Active or passive motor studies were carried out, depending on the hand function of the patient concerned. The active motor task consisted of sequential finger to thumb opposition, or fingers into palm movement (making a fist). The type of active task is thought to be important as more complex tasks have been shown to produce widespread activation in the motor system, whereas simpler tasks produce relatively weaker activation (Pujol et al. 1996). As a consequence, patients were encouraged to perform the finger to thumb sequential opposition task, and the simple task of movement of the fingers into the palm was only used in those patients who had deficits affecting fine finger movement or who had poorer concentration spans. Passive movement was used in patients with little or no motor ability in their hand. The passive movement paradigm is described in Section 7.2.4 of Chapter 7. In one patient (patient 5), fMRI was performed pre-surgically before EPI was implemented on the MR system. In this case, fMRI of active hand movement was carried out using FLASH imaging (TR 85 ms, TE 60 ms, pulse angle 40°, 64x128 matrix, interpolated to 128x128 matrix), with the same slice thickness and field of view as the corresponding anatomical images. Single slices were selected to cut through the sensorimotor cortex in the vicinity of the hand area and slices were tilted in a transverse to sagittal orientation.

9.2.2 Invasive studies

9.2.2.1 Cortical stimulation studies (during invasive monitoring and intraoperatively)

Cortical stimulation was carried out intra-operatively in four cases in this study. The stimulation was performed with bipolar forceps, with the stimulation intensity starting at around 5 mA and increasing stepwise, moving the point of stimulation each time until a response was obtained such as a motor twitch, sensations or arrest of speech. The position on the surface of the brain which evoked a response was recorded on the 3-D MR reconstruction in all three orthogonal planes for subsequent localisation (see Section 9.2.2.3 for method)

Invasive monitoring and cortical stimulation using subdural electrode grids was carried out in two patients. Chronically implanted subdural electrode grids were used which consisted of stainless steel disks embedded in a flexible sheet of medical-grade silicone. The electrode grids all had an inter-electrode distance of 10 mm and a contact diameter of 8 mm. The positions of a number of selected electrodes were registered on the 3-D MR reconstruction as described below (see Section 9.2.2.3). The patients underwent cortical mapping using the electrode grid to localise eloquent cortex which is to be avoided

during cortical resection. In this procedure, specific electrodes on the grid are stimulated bipolarly (in increments of increasing intensity until a response is observed, or after discharges appear in the ongoing EEG) and the patient observed for functional responses (among others Goldring, 1978; Gregorie & Goldring, 1984; Lesser et al. 1987; Wyllie et al. 1988; Duchowny & Jayakar, 1993). Although there is a risk of causing epileptiform activity, this method at present appears to be the most practical, particularly with children, as patient co-operation need not be required and there is little discomfort.

9.2.2.2 SEPs recorded during invasive monitoring

Goldring et al. (1970) first advocated a two-stage procedure in which a standard fixed electrode grid is first implanted and then utilised under non-operating room conditions to record SEPs. In this study, SEPs were recorded to map the sensorimotor cortex in one of the three patients who had subdural electrodes implanted. The left and right median nerve were stimulated at the wrist above motor threshold (at M+S intensity, see Section 4.2 of Chapter 4). Continuous EEG was acquired (using a bandwidth of 0.05-200 Hz, amplified at x12500, and digitised at 5 kHz), during which electrical stimuli were delivered. At least two runs were collected to ensure reproducibility. Averaged files were constructed from at least 200 accepted epochs (-10 to 150 ms duration) with an artefact rejection criterion of $\pm 100\mu V$ and channels were corrected using pre-stimulus baseline (-10 to 0 ms), using Neuroscan version 3.2. When recording directly from the cortical surface, the potentials are generally of high amplitude in a well circumscribed area. Therefore, any electrode relatively distant from the central fissure can be used as a reference electrode. In these cases the reference was selected in an inactive area on the electrode grid or on a strip array distant to the rolandic region. In addition, the ground electrode was ensured to be distant to the active cortical area. Topographical 2-D voltage maps were constructed of the first positive component (known as the P30) in the waveform.

9.2.2.3 Localisation of points intraoperatively on the MR scan

Subdural electrode grids now provide a standard technique for investigating epileptic activity in the brain; however there has been few reported studies of methods for the precise localisation of these grids on the surface of the brain. Localisation of the subdural electrode grids is particularly important for the neurophysiologist in identifying the underlying cortical area initiating the epileptic activity and regions of functional

cortex. Knowledge of the location of the grid on the surface of the brain will also aid the neurosurgeon intra-operatively during the resection of any identified epileptogenic tissue once the grid is removed.

In this investigation, a method to localise the subdural grid and intra-operative cortical stimulation positions on an MRI scan of the patient's brain was developed as described below. In addition, the regions of activation identified using fMRI studies were also located on the 3-D reconstruction for intra-operative use by the neurosurgeons. The positions of strategically chosen electrodes on the grid, of cortical stimulation, or of fMRI activations were saved as point locations on the surface of the brain on the MRI scan. Details of the method are described below:

1. Firstly, the scalp surface of the patient was registered to a 3-D whole head MRI scan immediately before the operation began, using a frameless stereotactic technique (either the ISG Viewing Wand system or Philips Image Guidance System). In this procedure, MR images (128-slice MPRAGE scan acquired sagittally, TR=9.7 ms, TE=4 ms, flip angle=12°, FOV: 250 mm, effective slice thickness=1.25 mm) were transferred to the Wand or Guidance system where the data could be reformatted and displayed in three orthogonal planes or as 3-D surface objects. In the operating room, the patients' head was fixed in position using a Sugita headholder and pins, and the articulated arm of the system was attached to the headholder. The arm was then calibrated and the patient's position relative to the arm was registered using surface landmarks such as the lateral and medial canthal margins and the anterior tip of the tragus on each side. These surface landmarks were then correlated with the same points on the 3-D MRI reconstruction of the skin. After this, over 80 random surface points on the face and scalp were touched with the probe, allowing the computer to generate a best-fit analysis of these landmarks to the 3-D image. Each point was assigned an error based on this fit, and a root mean square error calculated. During the procedure, precautionary re-registration was carried out using 4 points around the edge of the craniotomy to ensure that the head had not moved with the turning of the scalp flap.

2. Secondly, a reconstruction of the MRI of the brain was produced (this may be done outside the operating theatre, before surgery begins). This reconstruction involved segmentation of the brain from overlying structures (such as the skin and scalp) using an automatic tracing method based on interactive growing in individual MRI slices. A pre-specified selection threshold was set and a seed point placed within the brain. The brain was then isolated using a 2-D region-growing method which outlines the surface of the brain using the signal intensity difference between brain tissue and the scalp in the

image. At points where the threshold would not separate brain from background, it was necessary to trace those portions of the brain surface manually. This procedure was carried out in all of the 128 serial sagittal slices, and a 3-D reconstruction of the whole brain was subsequently created.

3. The results of intraoperative cortical stimulation studies were saved as positions in all 3 orthogonal planes on the MRI scan during the operation (see Figure 9.1). These positions could subsequently be relocated and visualised on the 3-D reconstruction after the operation. Using a similar method, the locations of subdural grids for invasive monitoring were superimposed on to the 3-D reconstruction (patients 1 and 2). In this method, a number of the electrode points were saved on the MRI scan in all 3 orthogonal planes and then relocated on to the 3-D reconstruction following the operation. Post-operative visual localisation of these electrode points and cortical stimulation results located on to a 3-D reconstruction of the MR images allows a direct comparison of the locations with respect to the whole brain and anatomical landmarks such as the central sulcus and sylvian fissure. In addition, these locations can be compared to areas of abnormal cortex which are also delineated and visualised on the 3-D reconstruction. The location of the subdural grid and cortical stimulation results were corroborated by means of the neurosurgeon's observations during the operation and/or skull x-rays obtained during the period of grid implantation.

4. The results of the fMRI were also visually superimposed on to the 3-D reconstruction of the brain for the neurosurgeon's use during the operation. This procedure involved the fMRI activations being displayed on contiguous sagittal images, and then drawing the activated regions on to the sagittal slices of the MRI before embedding the region within the 3-D reconstruction of the whole brain.

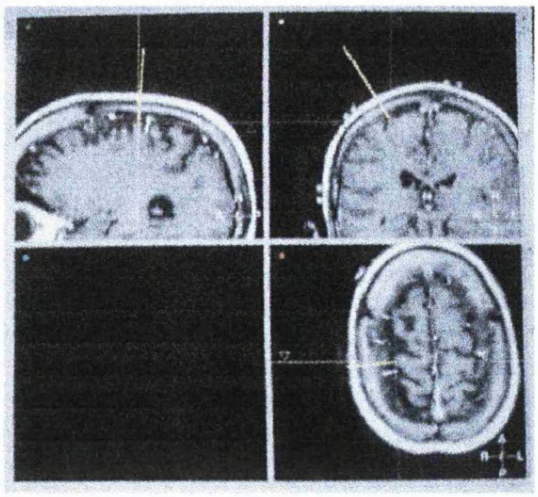


Figure 9.1: Example of a point on the surface of the brain identified on 3 orthogonal planes. The yellow line indicates the arm which the neurosurgeon holds and points to the brain, while simultaneously identifying the region on the MRI (such as a site inducing movement during cortical stimulation or an electrode position from a subdural grid). This point is relocated and visualised on the same MR image post-operatively and shown on the 3-D reconstruction.

There are several potential sources of inaccuracy of this technique for locating intra-operative points on to the 3-D reconstruction of the brain, which include the following:

- The localisation error between the initial co-registration of the MRI scan and the strategically placed landmarks on the surface of the head before surgery has begun.
- The technique can only be applied to subdural electrodes visible in the craniotomy.
- The localisation error between the location of the tip of the probe on to the electrode or area being marked.
- The accuracy of the post-operative location of the electrode point on the MRI re-placed on to the same data visually to allow superimposition on the 3-D brain reconstruction (there is anterior/posterior error only as the identical sagittal slice can be ascertained).
- The error involved in producing a 3-D region to represent the location of a single point on the brain surface.

9.3 Results

9.3.1 Summary of patients

A summary of the relevant clinical details in the 12 patients is shown in Table 9.1. Nine of the twelve patients had focal lesions in the vicinity of the sensorimotor cortex. As a result of the level of co-operation required from the patient in order to complete the fMRI examination, the youngest patient who participated in the study was 9 years old. The time between the onset of epilepsy and the investigation varied widely in the patient group (ranging from less than 4 weeks to 14 years).

Patient	age at first seizure (yrs.mnths)	pathology	location of lesion	acquired or congenital	side of damage	age at time of investigation (yrs.mnths)
1 (VD)	15.0	neurocystercerosis (parasite resides as calcified lesion)	within central sulcus, very close proximity to anatomical hand sensorimotor area	acquired	left	17.0
2 (VC)	9.0	atrophy, possible iscaemic lesion	insular cortex - back of sylvian fissure	acquired	right	14.0
3 (DE)	9.0	DNET	inferior parietal lobe, within sylvian fissure	acquired	left	9.0
4 (KP)	10.0	Rasmussen's encephalitis	frontal atrophy	acquired	right	17.0
5 (WJ)	2.9	low grade astrocytoma	frontal lobe, immediately anterior to precentral gyrus	congenital	left	14.0
6 (SS)	9.0	Rasmussen's encephalitis	diffuse throughout hemisphere	acquired	right	10.0
7 (TM)	9.9	DNET/low grade glioma	post-central gyrus of inferior parietal lobe	acquired	right	10.5
8 (MW)	3.0	cortical malformation - unknown origin	fronto-parietal region - diffuse	congenital	right	17.0
9 (TW)	9.1	low grade parencymal tumour, possibly astrocytoma	posterior frontal lobe	acquired	left	10.9
10 (AT)	14.0	low grade astocytoma	occipital and posterior parietal lobe	acquired	left	16.5
11 (SD)	9.6	vascular malformation	medial portion of hemisphere to pre-central gyrus	congenital	left	13.0
12 (AB)	2.0	cortical dysplasia	diffuse throughout hemisphere	congenital	right	16.0

Table 9.1: Summary of patient details (DNET = disembryoblastic neuroepithelial tumour).

Patient	summary of motor function	motor studies performed	hand fMRI location compared to normal side	distance of hand activation from lesion	comments	Other studies performed
1 (VD)	normal	active index finger+hand+ thumb+wrist	similar	9mm inferior	fMRI activation from all tasks similar in location	inv. monit. + intra-op cort. stim.
2 (VC)	normal	active hand+foot	similar	2.5cm superior	motor seizures involving hand and foot	inv. monit.
3 (DE)	normal	active hand	similar	3.5cm superior		
4 (KP)	poor strength, shakes when used	passive hand	i/l activation from normal hand	no focal lesion	i/l activation due to twitching of c/l hand	intra-op cort. stim.
5 (WJ)	normal	active hand	similar	2-3cm posterior	similar results seen post-operatively	intra-op cort. stim.
6 (SS)	normal	active hand, leg and foot	similar	no focal lesion		
7 (TM)	normal	active hand	predominantly i/l activation in similar location to normal c/l	1.5cm superior	reorganisation - i/l pathways recruited	inv. monit.
8 (MW)	left hemiparesis	passive hand	no activation			
9 (TW)	normal	active hand	similar	1cm posterior	focal tumour with large region of surrounding oedema impinging on motor strip	intra-op cort. stim.
10 (AT)	normal	active hand	similar	3-4cm anterior		
11 (SD)	normal	active hand	similar	1cm lateral		
12 (AB)	mild left hemiplegia	passive hand	similar	no focal lesion	S-11 activation also	

Table 9.2: Summary of patient and fMRI results (i/l = ipsilateral, c/l = contralateral, intra-op cort.stim.=intra-operative cortical stimulation, inv.monit.=invasive monitoring).

The choice of fMRI investigations to be carried out in the patient was dependent on the functional ability of the patient's hand contralateral to the affected hemisphere. As seen in Table 9.2, nine of the twelve patients exhibited normal sensorimotor function in the hand contralateral to the affected hemisphere and these patients were all able to perform active movement tasks. Three patients carried out passive movement tasks due to a mild to severe hemiparesis in the affected limb (patients 4, 8, and 12). In most cases the fMRI activated regions were similar in location in the homologous contralateral primary sensorimotor cortex following movement of the left and right hand. One patient did not demonstrate fMRI activation with movement of either the normal or affected hand (patient 8). The location of the peak activation in eight patients who showed fMRI activation and a discrete brain lesion was found to be between 1 to 4 cm distant from the site of the lesion (mean distance = 2.05 cm). In more co-operative patients, and if the

lesion was small and particularly close to the sensorimotor strip, several fMRI investigations were carried out.

A summary of the outcome in patients who subsequently underwent surgical intervention for their epilepsy is shown in Table 9.3.

Patient	functional outcome	correlation of fMRI with invasive studies?
1 (VD)	no deficit	Y
2 (VC)	no deficit	Y
3 (DE)	awaiting surgery	
4 (KP)	no change in severity of weakness	Y
5 (WJ)	no deficit	
6 (SS)	awaiting surgery	
7 (TM)	no deficit	Y
8 (MW)	awaiting surgery	
9 (TW)	no deficit	motor hand area not found intraoperatively
10 (AT)	no deficit	
11 (SD)	awaiting surgery	
12 (AB)	awaiting surgery	

Table 9.3: Summary of post-operative findings.

9.3.2 3-D MRI reconstructions of the brain

In this study, 3-D reconstructions of the brain were carried out in four patients using the procedure described in Section 9.2.2.3. In three patients, the results of intraoperative cortical stimulation studies were registered on the 3-D reconstruction (patients 2, 4, and 9). In two patients, the locations of subdural grids for invasive monitoring were superimposed on to the 3-D reconstruction (patients 1 and 2). In all cases, the root mean square error for the intraoperative registration between the brain and the MRI was below 2.5 mm.

9.3.3 Results of individual patients

Results from eight of the patients are shown in detail below.

9.3.3.1 Patient 1

Patient 1 is a female who presented with partial motor seizures involving an alternating rhythmic grasping and releasing motion of her right hand. Computed tomography and MR imaging revealed a single focus of calcification in the cortex of the left hemisphere, embedded within the central sulcus. As her seizures were refractory to medical treatment, she was considered for epilepsy surgery. fMRI studies were carried out to localise the hand sensorimotor area. Due to the likelihood that the hand area was in close proximity to the lesion site (given the presentation of partial motor seizures in the hand), a number of hand motor studies were performed. Four studies were carried out, which consisted of a flexion/extension movement of the wrist, the fingers, the index finger and thumb opposition (Figure 9.2). In all four studies, the peak activation was similar in location, situated within the central sulcus at the level where a 'hook' is seen in the axial image (the reported site of the hand sensorimotor area, see Chapters 1, 2 and 6). The lesion was not clearly visible on a T_1-weighted image but was seen clearly as a region of focal hypointensity on the EPI images acquired for fMRI purposes. Superimposition of the fMRI activation on to a base EPI scan revealed the lesion to be 9 mm superior to the location of activation (Figure 9.3) in the coronal view.

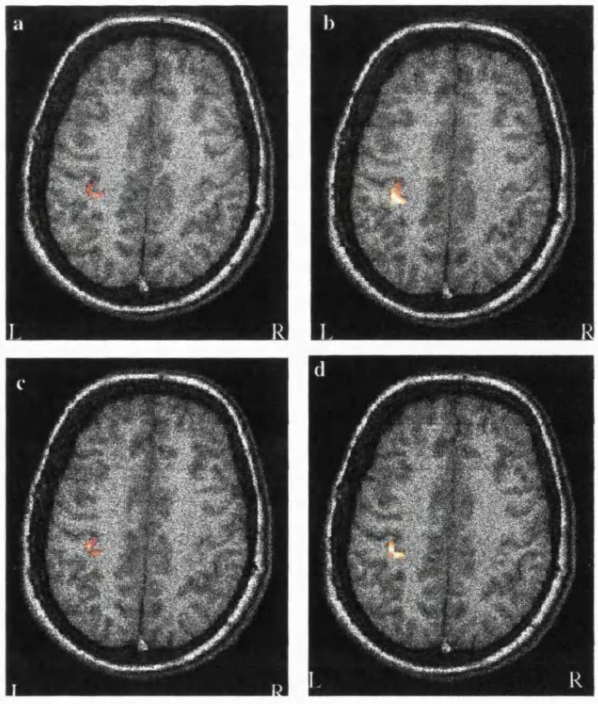


Figure 9.2: Patient 1. fMRI activation on active movement of the right wrist (a), hand (b), index finger (c) and thumb (d).

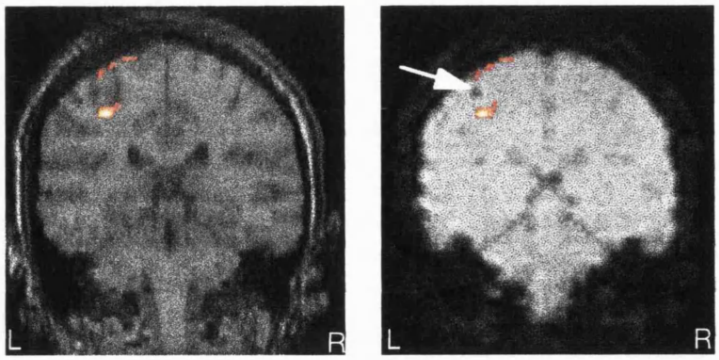
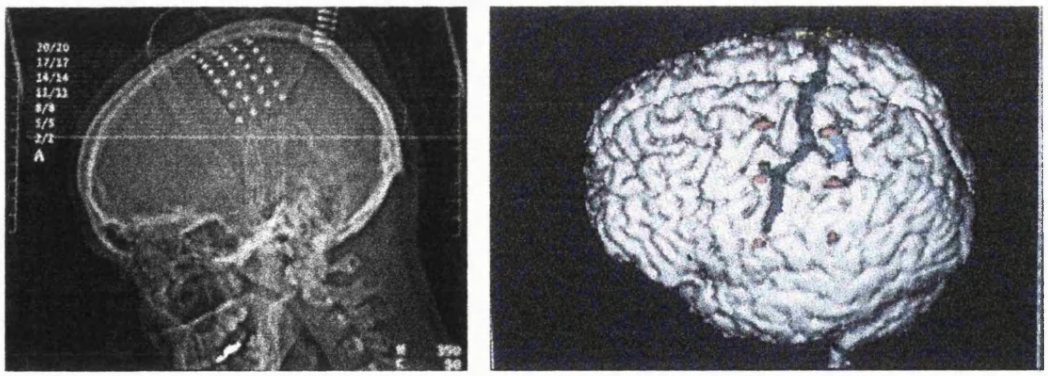


Figure 9.3: Patient 1. Coronal sections through the sensorimotor cortex transecting the lesion. fMRI activation is seen both deep within the cortical tissue and superficially (most likely venous drainage). The lesion is not easily seen clearly on the T1-weighted image, but is clearly visible on the base EPI image immediately above the site of deep activation (arrow).

It was postulated that the radiologically visible lesion was the epileptogenic focus but invasive EEG monitoring, using a subdural grid, was carried out for confirmation. The patient underwent invasive monitoring over a 3 day period prior to surgery. The location of the grid was determined by CT and more accurately on the surface of the brain by the method described in Section 9.2 (Figure 9.4).



a) b)

Figure 9.4: Patient 1. Methods to locate subdural plate. a) A CT scan of the plate in relation to the skull. b) 3-D reconstruction of the brain with the central sulcus indicated in dark blue. The six electrode contacts obtained from the subdural plate during implantation are superimposed on to the reconstruction (red), fMRI activation on active movement of the right hand is shown in light blue, and the location on the surface of the brain which evoked hand movement to cortical stimulation is shown on the precentral gyrus in green. In the right hemisphere, fMRI activation on active movement of the left hand is shown in yellow.

Invasive monitoring was carried out which demonstrated focal seizure activity in the region of the identified lesion. Invasive cortical stimulation using the subdural grid to

stimulate the cortex was also performed for mapping of the sensorimotor cortex beneath the grid. The location of the sensory and motor responses conformed with the pre-determined position of the grid, the central sulcus, and the primary sensory and motor cortices which were obtained during implantation of the grid (Figure 9.5).

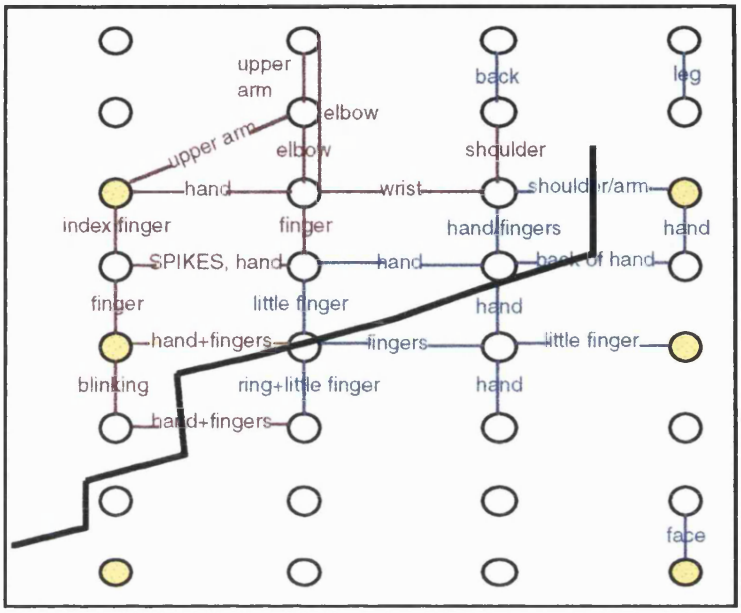


Figure 9.5: Patient 1. Stimulation of subdural grid electrodes (open circles). Circles shaded yellow indicate electrode positions obtained intra-operatively and used to locate grid on to brain 3-D MR reconstruction (Figure 9.1). Motor responses are shaded red, sensory responses are shaded blue. Central sulcus position is shown in black. Note that epileptic spikes were seen on the EEG in the region of the hand motor cortex.

During removal of the subdural plate and lesion resection, the patient underwent intra-operative cortical stimulation. The neurosurgeon removed the calcified lesion by opening the central sulcus, parting the pre- and post-central gyri. After removal, direct stimulation of the region of cortical tissue below the removed lesion resulted in a grasping movement of the right hand, similar in appearance to the finger flexion/extension movement performed during one of the fMRI studies (Figure 9.6). Immediately post-operatively, the patient suffered a transient loss of facility in her right hand which lasted less than a week after surgery. This was attributed to post-operative oedema and at investigations carried out 6 months post-operatively she was reported as having no functional deficits. She has subsequently remained seizure-free for over a year.

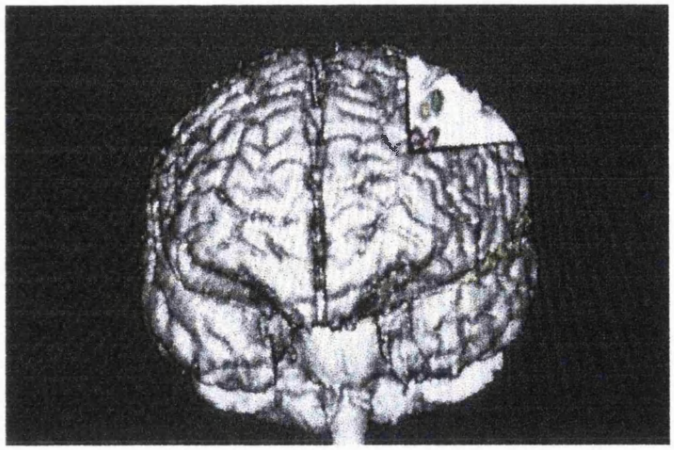


Figure 9.6: Patient 1. 3-D reconstruction of the brain viewed from the front with a section removed cutting through the central sulcus in the coronal plane. Regions shaded pink indicate fMRI activation on active movement of the right hand, green indicates the site of the lesion, and yellow shows the cortical area stimulated that produced hand movement intra-operatively after removal of the lesion. Laterally, the sylvian fissure is shown in yellow.

9.3.3.2 Patient 2

Patient 2 was revealed to have a lesion within the insula cortex, as seen in Figure 9.7, which was thought to be of ischaemic origin. He also had epilepsy, which involved motor seizures of the left arm and leg. Due to the pattern of his seizures, fMRI was performed to locate the hand sensorimotor area. The location of greatest activation was found to lie 2.5 cm superior to the site of the lesion.

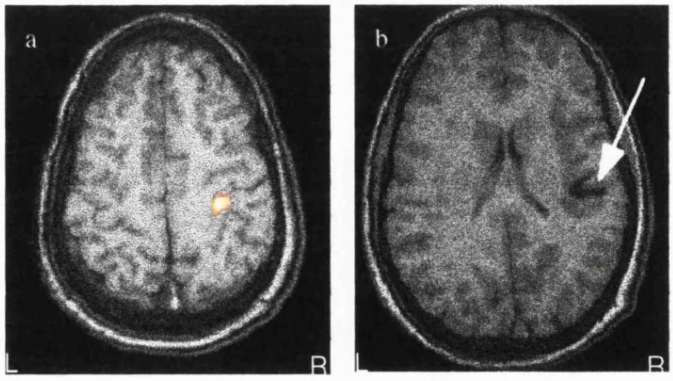


Figure 9.7: Patient 2. Contralateral fMRI activation in the sensorimotor cortex on active movement of the left hand (a). (b) demonstrates the site of the lesion deep within the sylvian fissure (arrow), in the region of the parietal operculum.

Invasive monitoring was performed to further investigate the origin of the seizures with a view to resecting the abnormal area. The position of the subdural grid in relation to the

brain was determined by obtaining the location of 13 electrode contacts from the grid during implantation and superimposing the electrode positions on to a 3-D MR reconstruction of the patient's brain (see Section 9.2.2.3 above). The central sulcus was then identified on the 3-D reconstruction and superimposed on to the subdural grid (Figure 9.8).

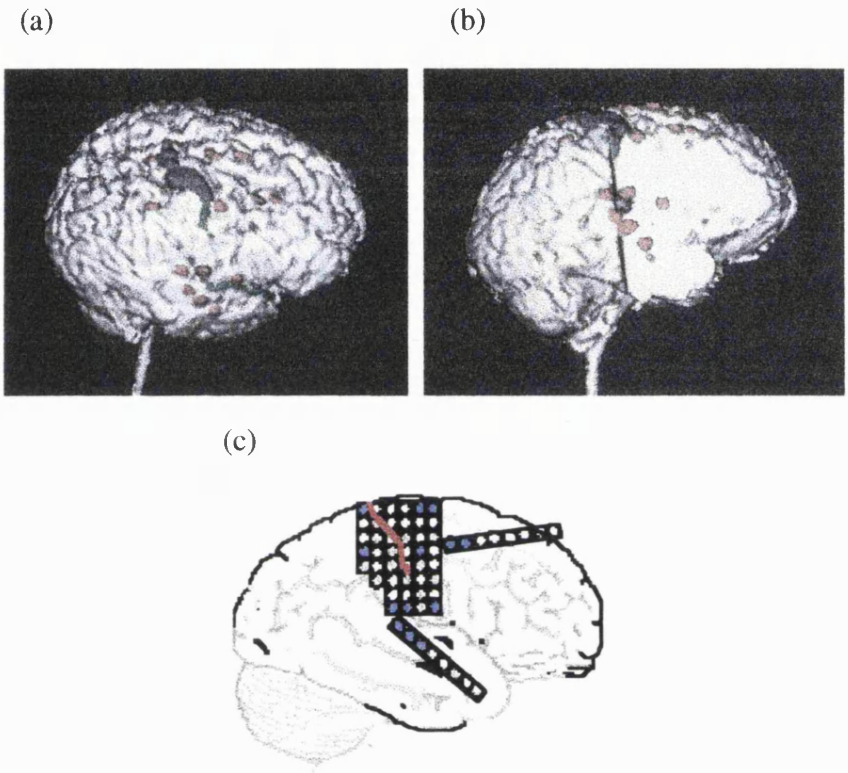


Figure 9.8: Patient 2. (a) 3-D reconstruction of whole brain MR with intra-operative electrode positions identified in red, central sulcus and sylvian fissure shown in green and superimposed fMRI activation in dark blue seen on the surface of the brain. (b) Section removed to show location of lesion within the sylvian fissure relative to the electrode locations (fMRI activation superimposed in dark blue indicated by an arrow). (c) The results of the electrode locations (blue) over the whole plate in relation to the central sulcus (red) are overlaid on to a schematic representation of the brain.

SEPs to median nerve stimulation were carried out to locate the hand sensorimotor area and relate the findings to the location of the fMRI activated region. The peak early SEP response following stimulation of the contralateral (left) side was located immediately posterior to the central sulcus, as seen in the 2-D voltage map showing the first positive component in the waveform (Figure 9.9). In addition, SEPs in response to stimulation of the ipsilateral (right) median nerve were recorded. Ipsilateral responses were obtained on the subdural grid, the location of the peak early SEP response being similar to that from stimulation of the contralateral side (Figure 9.10). The early ipsilateral SEP

response was smaller in amplitude and longer in latency compared to the early component of the contralateral response.

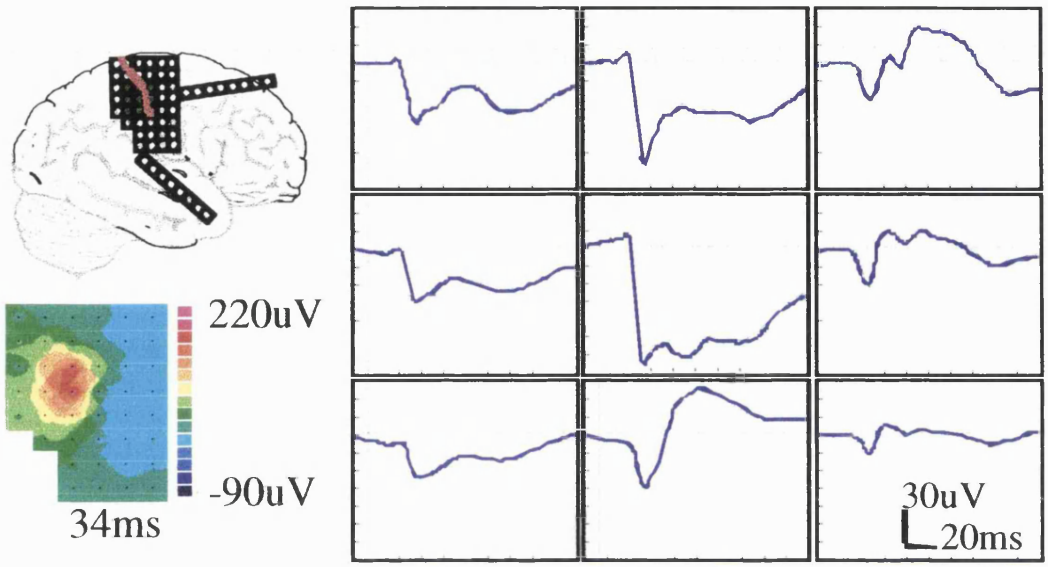


Figure 9.9: Patient 2. The right of the figure shows the SEP responses (from electrodes shaded green on the schematic of the brain) to stimulation of the left (contralateral) median nerve. A 2-D voltage map of the earliest positive scalp response at 34 ms is shown in the bottom left of the figure. The position of the central sulcus is demarcated in red.

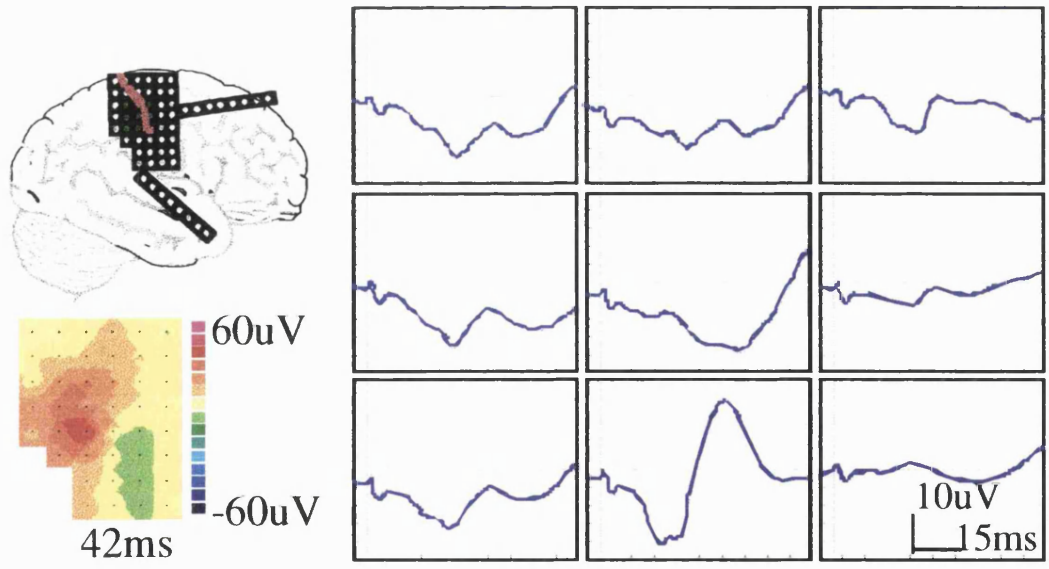


Figure 9.10: Patient 2. The right of the figure shows the SEP responses (from electrodes shaded green on the schematic of the brain) to stimulation of the right (ipsilateral) median nerve. A 2-D voltage map of the earliest positive response at 42 ms is shown in the bottom left of the figure. The position of the central sulcus is demarcated in red.

During the invasive monitoring period, cortical stimulation studies were also carried out to determine the epileptogenic zone in the brain, and the location of the sensory and motor strip in relation to this area. The representation of many body parts could be mapped on to the cortical surface, providing further valuable data for surgery. The location of the thumb motor area on stimulation of the electrode grid was in a similar region to the location of the SEP responses (Figure 9.11). The locations of the thumb, face and shoulder movement were found anterior to the central sulcus, in accordance with Penfield's functional map of the representation of body parts in the primary sensorimotor cortex (Penfield & Boldrey, 1937). Lip sensation was induced from stimulating electrodes immediately posterior to the site where face movement was produced (posterior to the central sulcus). In addition, the peak response from stimulation of the contralateral median nerve was located posterior to the electrodes inducing thumb movement.

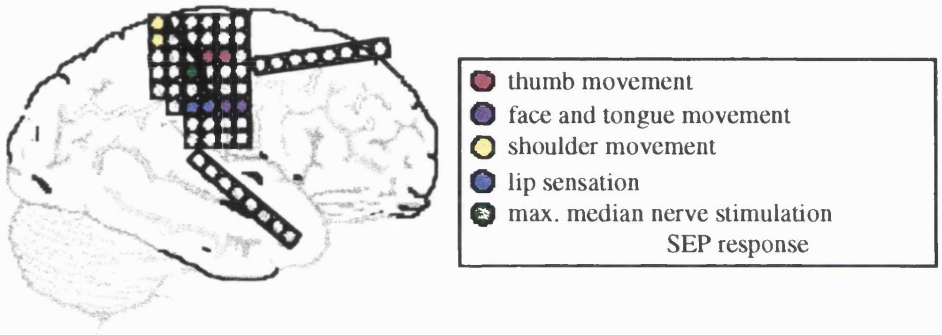


Figure 9.11: Patient 2. Results of grid stimulation studies and maximal locations of the SEP response to the contralateral median nerve.

At the end of the invasive monitoring, the patient underwent a resection of the lesion in the insula cortex. Post-operatively he had no sensorimotor deficit in his arm or leg; however he still suffers from epilepsy, which was unfortunately unchanged with regard to frequency and severity compared to pre-operative levels.

9.3.3.3 Patient 4

Patient 4 first presented with left-sided epilepsy at the age of 10 years. The subsequent MRI revealed right hemisphere atrophy in the frontal lobe, and she was suspected of having Rasmussen's encephalitis. At the time of the fMRI investigations, she had a slight weakness in her left hand and arm, which displayed constant twitching when she attempted to use it. However, she was able to reduce the twitching by relaxation. fMRI was thus performed using a passive movement task to identify the hand sensorimotor area. Activation was located in the vicinity of the 'hook' of the central sulcus, known to be the site of the hand sensorimotor cortex from previous studies (refer to Chapter 2). Intra-operatively, a biopsy was taken (confirming Rasmussen's encephalitis) and subpial transections performed over the sensorimotor area of the brain. Intra-operative cortical stimulation was carried out to confirm the fMRI findings and identify the central sulcus on the exposed surface of the brain (Figure 9.12). Post-operatively there was unfortunately no improvement in her epilepsy. However she also did not suffer any further reduction in her hand sensorimotor ability.

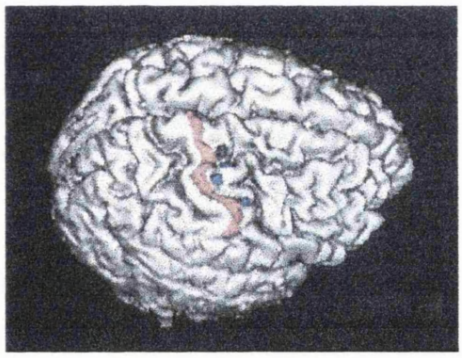


Figure 9.12: Patient 4. Intra-operative cortical stimulation results superimposed onto 3-D brain reconstruction. Areas shaded light blue indicate the sites evoking epileptogenic activity, yellow indicates the site of shoulder movement, dark green the site of finger movement, and green (just above light blue shaded area) the site of thumb movement. The central sulcus is indicated in red.

9.3.3.4 Patient 5

Patient 5 suffered from a left frontal astrocytoma which resulted in complex partial motor seizures in the right side of his body. He underwent fMRI investigations to locate the hand sensorimotor cortex and to compare the site of the activation with the location of the lesion. Pre-operatively, activation was seen posterior to the lesioned site, in both the central and post-central sulcus (Figure 9.13). The region of activation in the central sulcus was 2-3 cm behind the posterior boundary of the tumour as seen on the T_1-

weighted axial image. Intra-operative cortical stimulation was carried out to identify the cortical surface areas which evoked face, arm and hand movement. The tumour was subsequently removed and the patient did not suffer any sensorimotor deficits post-operatively and remains seizure-free. fMRI investigations were subsequently carried out 6 months post-operatively, with activation again located in the contralateral hemisphere within the central and pre-central sulcus (Figure 9.13). This corroborates the pre-operative fMRI findings and suggests that the motor cortex has indeed remained functional and anatomically intact following surgery.

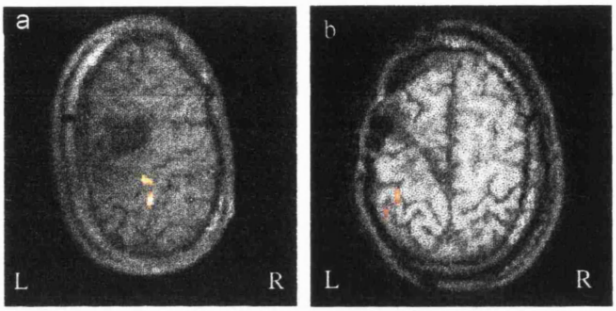


Figure 9.13: Patient 5. fMRI activation following active movement of the affected hand. Pre-operatively, data were acquired on a tilted axial image through the sensorimotor cortex of the affected hemisphere (a) (see Section 9.2.1). Post-operative results are shown in (b). In both images, the activation can be seen within the central and post-central gyrus posterior to the lesioned and removed site.

9.3.3.5 Patient 7

Patient 7 was referred for fMRI investigations following the recent onset of intractable partial motor seizures and the radiological identification of a space-occupying lesion in the post-central gyrus of the inferior parietal lobe (possibly a DNET). fMRI was carried out using an active movement task of the left and right hand. Activation was seen only in the unaffected hemisphere in response to movement of either hand (Figure 9.14). There was no fMRI activation seen in the sensorimotor cortex of the affected hemisphere with either the left or right hand motor task. Ipsilateral activation on movement of the affected (left) hand was very similar in location to the contralateral activation on movement of the unaffected (right) hand. This activated region in the left hemisphere was found to be 1.5 cm superior to the level of the lesion in the right hemisphere. These findings suggest that the sensorimotor cortex in the unaffected hemisphere is contributing to the movement of the affected (ipsilateral) hand. This ipsilateral sensorimotor cortex contribution appears to be greater than that of the sensorimotor cortex in the contralateral hemisphere.

The patient underwent invasive monitoring and surgery with removal of the tumour. Normal contralateral SEPs were recorded during the invasive monitoring to left median nerve stimulation at the wrist. Post-operatively he did not demonstrate a sensorimotor deficit in the contralateral side of the body and is currently seizure-free.

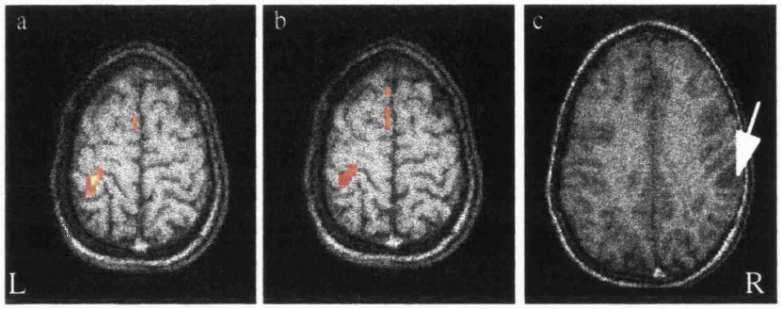


Figure 9.14: Patient 7. fMRI activation following movement of the right and left hand in the contralateral (a) and ipsilateral (b) primary sensorimotor cortex. The site of brain lesion (DNET) is indicated by an arrow (c).

9.3.3.6 Patient 9

Patient 9 did not have a sensorimotor deficit in the limb contralateral to the affected hemisphere pre-operatively. However, imaging investigations revealed a posterior frontal tumour and surrounding oedema located immediately anterior to the pre-central gyrus. fMRI investigations were performed using a hand motor task and activation was seen in the central sulcus, approximately 1 cm posterior to the lesion (Figure 9.15). Given the close proximity of the lesion to the motor strip, intra-operative cortical stimulation was also carried out. An unusual distribution of functional tissue was demonstrated in the region of the sensorimotor cortex on the surface of the brain. Stimulation of the cortical surface pre-centrally did not result in a hand motor response. However, sensation in the hand occurred with stimulation of the superior post-central gyrus. In addition, stimulation of the mid-portion of the precentral gyrus caused speech arrest, which was not reported to be characteristic of an inability to move the facial muscles, and suggests the site of Broca's area. With these findings, the neurosurgeon decided to proceed with a much more restricted resection of the core of the tumour. Post-operatively the patient suffered no sustained sensorimotor deficit and is currently seizure-free.

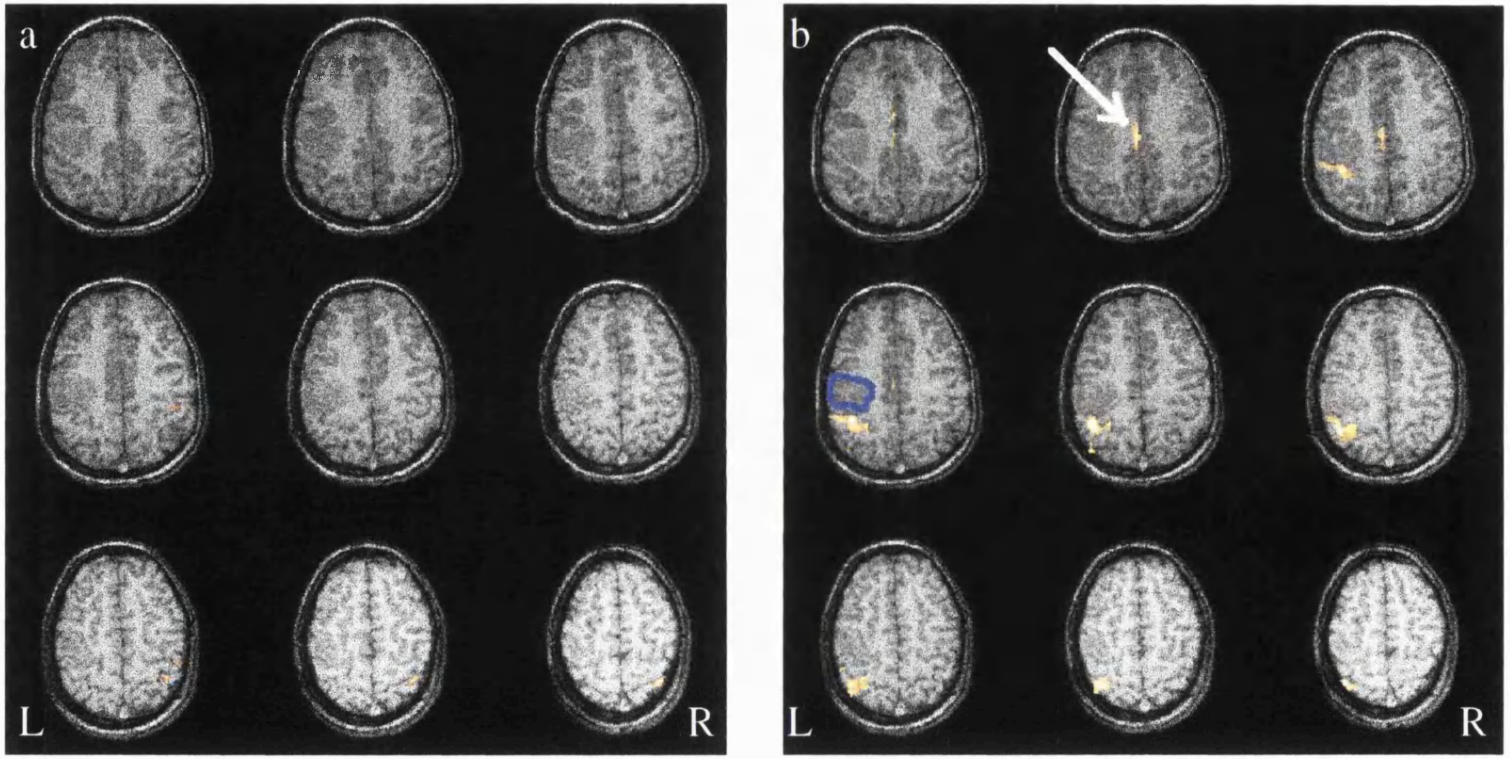


Figure 9.15: Patient 9. fMRI activation in the contralateral primary sensorimotor cortex on active movement of the normal left (a) and affected right (b) hand. The approximate boundary of the lesion is demarcated in one slice in blue (b), but can be seen to extend over many slices. Activation was also seen in the region of the SMA area, indicated by the arrow (b).

9.3.2.7 Patient 11

Patient 11 was found to have a left frontoparietal arteriovenous malformation following a four year intermittent history of right-sided weakness affecting her legs more than her arms. Neuropsychological testing of her sensorimotor function showed that there was no obvious discrepancy between fine motor co-ordination skills of her left and right hand. MR imaging revealed that the arteriovenous lesion lay in the frontoparietal region on the medial aspect of the left hemisphere (Figure 9.16). fMRI was carried out to locate the hand, foot and leg sensorimotor cortex and compare the site of the activation with the boundary of the lesion (Figure 9.16). The foot motor task was clenching and unclenching of the toes and the leg task was rotation of the leg at the hip. However, the fMRI results of the leg and foot motor tasks had to be rejected because of movement artefact. Activation with respect to the active hand task was found in the contralateral central sulcus, approximately 1cm lateral to the lateral border of the lesion. Activation was also seen immediately anterior to the lesion site, in the region of the SMA.

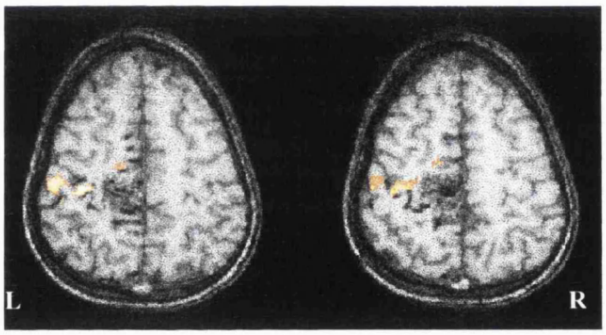


Figure 9.16: Primary sensorimotor cortex activation in the left hemisphere on active movement of the right hand. Two adjacent axial slices (3mm thick) are shown. Medial to the activation, extending to the longitudinal fissure, is the vascular malformation.

9.3.2.8 Patient 12

Patient 12 was diagnosed as having neurofibromatosis in the right hemisphere at the age of two years, at which time he had also started having partial seizures. His previous MRI was reported to show a small right hemisphere and slight enlargement of the right lateral ventricle, with cortex around the posterior part of the insula, inferior parietal and superior frontal regions appearing thick and smooth. He developed a mild hemiplegia in his left hand and fMRI was carried out following passive movement to identify the sensorimotor cortex. Activation in the primary sensorimotor cortex of the right hemisphere following passive movement of the left (hemiplegic) hand was located

within a sulcus which was comparable to that located in the left hemisphere following passive movement of the right (normal) side (Figure 9.17). fMRI activation was also found close to the midline, most likely indicating the SMA, and in a region immediately above the sylvian fissure, most likely the S-II area. Due to the cortical malformation polymicrogyria, the S-II area was found in non-symmetrical slices on passive movement of the left and right hand (S-II activation in the right hemisphere superior to S-II activation in the left hemisphere). Anatomically, however, the fMRI activation appears to lie within the parietal operculum in both hemispheres.

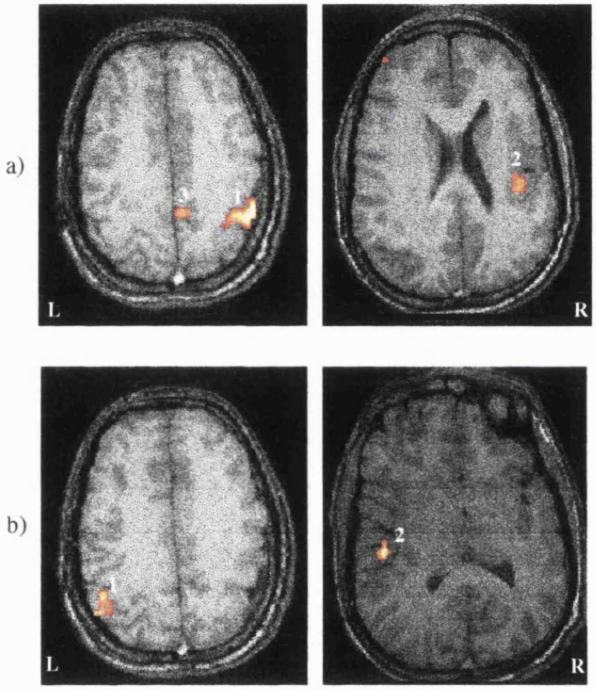


Figure 9.17: Patient 12. fMRI activation on passive movement of the left, hemiplegic (a) and right, normal (b) hand. Activation is seen in the contralateral primary sensorimotor cortex (1), and the second somatosensory area (S-II) (2), following passive movement of the hemiplegic and normal hand. Activation in the contralateral supplementary motor area (3) is also seen following passive movement of the hemiplegic hand.

9.4 Discussion

In this study, fMRI has been demonstrated to be a useful technique in locating the hand primary sensorimotor cortex in eleven out of twelve patients prior to neurosurgery. All of these patients had intractable epilepsy and unilateral brain damage in the vicinity of, or adjacent to, the cortical sensorimotor area.

A number of specific issues with respect to fMRI as a tool for pre-surgical mapping of the sensorimotor cortex are addressed below.

9.4.1 The use of fMRI in pre-surgical mapping of the sensorimotor cortex in children

The majority of studies that have used fMRI pre-surgically as a functional brain mapping technique have been carried out in adult patients (for example Jack et al. 1994; Latchaw & Hu, 1995; Atlas et al. 1996; Kahn et al. 1996; Mueller et al. 1996; Yetkin et al. 1997). Many of these previous studies have now demonstrated the value of fMRI in the localisation of functionally eloquent cerebral cortex, including motor, somatosensory, visual and language areas. This present study, in agreement with the previous studies in adults, demonstrates the use of pre-surgical fMRI in the localisation of the sensorimotor cortex in children with brain damage. There has been one previous study investigating the use of pre-surgical fMRI in the identification of the motor, sensory, visual and/or language cortex in a group of children under the age of 18 years (Stapleton et al. 1997). fMRI was successful in all patients in delineating the relationship between the lesion and the regions of task-activated cortex. In addition, frameless stereotaxy and direct cortical stimulation were also carried out in some or all of the patients, and the authors reported that a combination of all three techniques was most useful in accurately localising intracerebral lesions in eloquent brain, and to reduce morbidity of resecting these lesions in children. The youngest person they studied was 4 years old; however they reported that, in general, unsedated children under the age of 6 years may be difficult to study with fMRI. In addition, Chapman et al. (1995) carried out a pre-operative sensorimotor fMRI examination in one 15 year old patient with a seizure disorder related to a tumour in the SMA. The youngest child to undergo fMRI sensorimotor cortex mapping in the present study was 9 years of age. One patient (aged 17 years) failed to demonstrate fMRI activation on the motor task. However, this was most likely due to the patient having a hemiplegia and requiring the use of a passive movement task which may be

less reliable in activating the sensorimotor cortex in a hemiplegic limb, rather than this patient being less co-operative compared to other patients.

9.4.2 Comparison of fMRI with other functional brain mapping techniques

Cortical stimulation and/or invasive monitoring procedures were also carried out in 6 of the patients in the present study in order to identify the epileptogenic zone, or to confirm the location of the primary sensory and/or motor cortex. These 6 patients also underwent fMRI investigations for functional mapping of the sensorimotor cortex. In 3 of the patients, using superimposition of the results on to 3-D reconstructions of the brain, the surface location of the hand primary sensory and motor cortex and the central sulcus using the invasive methods was shown to be in close agreement with the location of the primary sensorimotor cortex activated on fMRI. This supports a number of previous studies, in which intra-operative mapping validated the accuracy of the fMRI results (for example Jack et al. 1994; Puce, 1995; Yousry et al. 1995; Pujol et al. 1996; Yetkin et al. 1997; Pujol et al. 1998).

In the remaining three patients, it was not possible to examine the relation between the findings from fMRI and other brain mapping techniques. In one case the results were not superimposed onto the 3-D reconstruction (patient 5), and in another case cortical stimulation failed to evoke a motor response, so a correlation with the fMRI could not be made (patient 9). In the third patient (patient 7), contradictory findings were obtained as the fMRI data demonstrated isolated ipsilateral sensorimotor cortex activation on movement of the affected hand, whereas contralateral SEPs were recorded to stimulation of the affected side during invasive monitoring. Invasive SEPs to stimulation of the normal hand were not investigated in this patient.

9.4.3 Methodological issues

There are a number of methodological issues in making comparisons between the invasive techniques described above for cortical mapping and non-invasive fMRI technique. These issues are discussed below.

A fundamental difference between the fMRI and cortical stimulation methods is that fMRI detects changes in flow in capillaries or veins draining a region of brain, whereas intra-operative cortical stimulation is based on changes in the polarisation of neurones

induced by an electrical current. As reviewed in Section 2.2.2 of Chapter 2, there has been controversy in the literature concerning whether the anatomical correlate of increased signal intensity detected by fMRI consists of veins or venules (such as Lai et al. 1993; Duyn et al. 1994). This issue is of crucial importance if fMRI is to be used as a technique to locate the site of eloquent brain areas and then compare these areas with the location of the brain lesion to be removed. In this study, activation was seen mainly within the area of the central sulcus, and also extended into the surrounding parenchymal structures in the pre- and postcentral gyri. It is likely that venules give rise to an increased signal intensity in the parenchyma, whereas the larger veins that drain this area are located in the adjacent central sulcus. In addition, due to the resolution of the fMRI images acquired here (3 mm isotropically), it is difficult to determine the location of an activated region accurately (for example, to determine if activation is situated within the pre- and/or postcentral gyrus). It is likely that the sulcal veins just described (in which the peak fMRI activation is located in the central sulcus) are fed by smaller veins or venules within the cortex of the adjacent posterior and anterior banks of the pre- and post-central gyri respectively. In addition, as described in Chapters 2 and 3, the BOLD effect becomes rapidly diluted away from the site of activation, and 3D EPI is relatively insensitive to inflow effects. We can be reasonably confident, therefore, that the activated region located within the central sulcus in these pre-surgical patients is from locally situated activating parenchymal tissue in the pre- and/or postcentral gyrus, which is controlling hand movement and sensation.

Another issue concerning fMRI and invasive methods of cortical mapping involves the location at which brain function can be mapped. Using invasive methods, only cortical tissue on the surface of the brain can be tested with a high degree of confidence, whereas activation deep within the brain is easily detected using fMRI. One study (Yetkin et al. 1996c) has measured the distance between the centre of gravity of the fMRI activation and the centre of the corresponding intra-operatively identified functional site on the brain surface and reported the distances to be approximately 15-20 mm in most cases. In agreement, the present study has also highlighted that caution must be adopted when interpreting functional responses recorded from the brain surface, as potentials recorded at the brain surface may originate from distant generators deep within the brain. The development of methods for determining the location of dipole sources from responses recorded from subdural grids will allow the identification of functional tissue deep within the brain in patients undergoing invasive monitoring (Cakmur et al. 1997). A correlation between the deep fMRI activation and cortical stimulation within the central sulcus was made in one case in this study (patient 1) (also reported in Holloway et al. 1999). In this case, stimulation immediately below the site of

the lesion (after resection) resulted in a hand clenching movement, similar to the task performed during one of the fMRI investigations. The site stimulated was approximately 0.5 cm above the superior margin of the fMRI activated region (as identified on the 3-D reconstruction intra-operatively). This verifies the presence of active sensorimotor cortical tissue deep within the brain using invasive and non-invasive techniques (that could not be identified by direct cortical stimulation prior to lesion resection), and the advantages of using fMRI to identify pre-surgically deep activated regions within the central sulcus.

One of the disadvantages of using pre-operative methods such as fMRI is the potential movement of tissues (relative to the time of functional imaging) that may occur in the operating room, as a direct result of the surgical intervention. In contrast, direct cortical stimulation can be applied to map the primary cortical regions with pathology intra-operatively. In an attempt to deal with this issue, recent studies have implemented an intra-operative MRI device that facilitates a non-invasive fMRI examination in the operating room (Gering & Weber, 1998; Maldjian et al. 1997). Not only will this intra-operative fMRI technique have the advantage of providing intra-operative correlation of vital cortical areas relative to the targeted pathology, but it may also alleviate the need for cortical exposure in excess of the specific surgical requirements. This is a promising advance in technology to assist the neurosurgeon during surgical procedures involving the resection of damaged tissue in the vicinity of eloquent cortex.

Invasive cortical mapping using stereotaxy has been identified as a beneficial and reasonably accurate technique in several previous studies (Drake et al. 1994; Stapleton et al. 1997). The technique is useful as it assists in locating the position of the bone flap in relation to the brain, the localisation of lesions deep to the cortex, and the determination of lesion margins in the depths of the brain. Frameless stereotaxy (as used in the present study) may ultimately reduce the total time of a neurosurgical procedure by providing the neurosurgeon with a greater confidence to more rapidly localise and aggressively resect large lesions than would be possible if the device were not used. The major disadvantage of all frameless stereotaxy systems is that they rely on data obtained from preoperative images and therefore become relatively inaccurate with brain shifts that may occur during an intracranial procedure.

There is currently great interest in neurosurgery in combining information from functional brain mapping techniques with stereotactic neurosurgical systems (Gallen et al. 1994; Rezai et al. 1997; Stapleton et al. 1997). In this present study, the integration of data from fMRI and ISG Viewing Wand or Philips Image Guidance System was

performed pre-operatively. The fMRI data were superimposed onto the anatomical MRI data on the stereotactic guidance system. Using this information, the neurosurgeon could then plan the optimum trajectory to the lesion to avoid the functional cortex. The fMRI data were then complemented by direct cortical stimulation in several patients to validate the functional data prior to lesion resection. As demonstrated in this study, recordings from subdural electrode arrays with contacts directly on the surface of the brain provide a reasonably accurate method for investigating the location and distribution of epileptogenic and functional neurophysiological data. Therefore it is imperative that the location of the grid on the brain surface is localised as accurately as possible. Previous studies have suggested that 3-D models representing the patient's brain may be useful for risk assessment and for planning surgical strategies (such as Cosgrove et al. 1996). In the present study, the location of sensory and motor areas were investigated using subdural electrodes, using a technique for the registration of the arrays onto 3-D MRI reconstruction of the cortex. The major advantages of the reconstructions are that they provide information regarding both the distribution of electrophysiological potentials relative to gyral patterns, and the location of pathology relative to the functionally activated areas of the cortex. Previously reported clinical investigations with subdural grid recordings have used a variety, or combination of, methods to locate the grid on the brain, such as intra-operative sketching or photography, neurosurgeon's observations and post-implant skull radiography (for example Lueders et al. 1983; Lee et al. 1986; Gevins et al. 1994). Several groups have sought more sophisticated methods to precisely localise subdural electrode positions onto cortical anatomy. One method for subdural grid location uses the 3-D digitisation of 2-D skull films taken of the grid in the head (Hoffmann & Esthappan, 1997) and Cartesian electrode locations fitted until a least squares fit is obtained (Darcey & Williamson, 1985; Pelizzari et al. 1989; Grzeszczuk et al. 1992; Gevins et al. 1994; Towle et al. 1995, 1998). Another study by Uematsu et al. (1992a) determined the position of their arrays photographed intra-operatively in relation to the 'rolandic line' (following the presumed central sulcus) using cranial landmarks on lateral skull x-rays, and a second technique using the identification of the central sulcus on the patient's MRI scan. Visual comparisons between the photographed locations on the cortical surface and MRI/X-ray surface reconstructions were then made. Perhaps the most accurate method has been developed by McCarthy et al. (1991) to identify stainless-steel electrodes on MR images, so allowing direct localisation of the grid as locations determined in the Talairach co-ordinate system on the MRI (Allison et al. 1996). In the present study, stainless steel electrodes were not used, and so another method for grid localisation was developed. The method is essentially similar to that of Allison et al. (1996); however the locations of the electrodes are recorded intra-operatively directly on the MRI, so allowing little

room for human error with re-location of those points onto the same MRI scan post-operatively. Further research into improving the registration of invasive electrophysiological findings on MR images is necessary to provide a more accurate common metric to localise intracerebral lesions in the eloquent brain, and to reduce morbidity when resecting these lesions in children (Detre et al. 1995).

This study has shown that fMRI may be used as one method to localise regions of eloquent cortex; however it is imperative to support the results with other invasive and non-invasive techniques such as PET, MEG, TMS, pre-operative subdural mapping or intra-operative cortical stimulation. Indeed, methods such as PET (Seitz et al. 1995; Vinas et al. 1997), MEG (Sobel et al. 1993; Rezai et al. 1997), and TMS (Morikawa et al. 1998) have been used to locate the hand sensorimotor area in patients with focal cerebral lesions (or a combination of these techniques; see for example Baumann et al. 1995; Morioka et al. 1995; Wunderlich et al. 1998). In addition to locating functional areas of the brain in patients pre-surgically, fMRI has been used to map the cortical activation that occurs during focal seizures (for example Jackson et al. 1994; Detre et al. 1995). The development of such techniques, in particular to identify interictal or subclinical events, will undoubtedly enhance the use of fMRI in locating functional and epileptogenic tissue, further reducing the need for invasive methods in pre-surgical evaluation, which will in turn decrease patient morbidity.

9.4.4 Reorganisation of sensorimotor function

Inter-hemispheric reorganisation was suggested to have occurred in one patient (patient 7). Ipsilateral cortical activation following hand movement of the affected side was demonstrated using fMRI, with no activation visible in the contralateral hemisphere. There have been a number of other fMRI studies reporting pre-surgical cases of inter-hemispheric reorganisation as a result of unilateral brain damage. Unlike this study, however, the majority of these studies demonstrated that ipsilateral sensorimotor cortex activation was present in the unaffected hemisphere in addition to contralateral activation in the affected hemisphere (Roux et al. 1997; Yoshiura et al. 1997; Caramia et al. 1998; Fellner et al. 1998; Harrington & Downs, 1999; Hemple et al. 1999; Kollias et al. 1999). In the patient in the present study, it is plausible that ipsilateral sensorimotor cortex had increased in activity to subserve function in the limb contralateral to the damaged hemisphere. Such reorganisation has been described previously in this thesis in paediatric patients following hemispherectomy and stroke (refer to Chapters 7 and 8, respectively). For the patient in this study, such findings were surprising given the

location of the lesion which was situated within the insula cortex. The large distance between the location of the lesion and the hand sensorimotor area (3-4 cm) would suggest that the functional sensorimotor cortex would not be affected by the lesion. As ipsilateral fMRI activation in control subjects was only demonstrated in a hand active motor task in the presence of normal contralateral activation, this suggests that the sensorimotor area in this patient must have sustained damage, thus promoting functional reorganisation of the sensorimotor system. This is possibly due to the effects of seizures which spread from the lesion site to the primary sensorimotor area. However, the ipsilateral sensorimotor cortex fMRI activation demonstrated in patient 7 does not rule out there being contralateral (damaged) sensorimotor cortex activation during the task, since the intensity of activation may be below the sensitivity of the technique. Indeed, the recording of contralateral SEPs during invasive monitoring makes this theory most likely. Nevertheless, it remains the case that the ipsilateral fMRI activation was significantly greater than any possible undetected contralateral activation. These data highlight the application of pre-surgical non-invasive fMRI for not only mapping the sensorimotor cortex, but also for identifying possible regions of cortical reorganisation of sensorimotor function.

None of the patients in this study demonstrated intra-hemispheric reorganisation. In each case, the peak activation was located in the anatomical hand area within the central sulcus. The topic of intra-hemispheric reorganisation has been previously discussed in Chapters 7 and 8 in relation to hemispherectomised patients and patients with infarcts. In contrast to the findings in presurgical patients in this study, there have been several reports in the literature of altered or shifted sensorimotor areas as a result of brain damage or lesions. For example, Yousry et al. (1995) reported that the fMRI activation in the motor hand area was broader and more diffuse in four of their six patients with space-occupying lesions in, or adjacent to, the precentral gyrus compared to normal controls. In addition, a number of other studies using fMRI and PET techniques have demonstrated intra-hemispheric plasticity in the sensorimotor cortex, with sensorimotor regions being shifted distances of up to 43 mm away from the original site (Seitz et al. 1995; Wunderlich et al. 1998). Kollias et al. (1999) also demonstrated large scale reorganisation both in terms of a shift in the cortical representation of the primary sensorimotor cortex and increased activation in secondary association areas (such as the premotor and supplementary motor areas). These studies indicate that discrete brain lesions may induce local and distant sites of cortical reorganisation in the representation of hand muscles, the pattern of which appears to be unique in each patient. These data highlight the importance of considering individual differences of intra- as well as inter-

hemispheric cortical reorganisation of function in the study of brain plasticity in patients prior to neurosurgery.

Invasive recordings using closely spaced electrodes on the surface of the brain provide accurate temporal measurements of the human cortical surface electrical activity. The spatial resolution of invasive SEP recordings is also improved compared to scalp SEP recordings, as the electrodes are more closely spaced together and the cortical potentials are not smeared by volume conduction through the skull and scalp. As a consequence, the cortical potentials that originate close to the cortical surface are likely to be highly localised to electrodes directly overlying the active region. In one case, electrical stimuli were applied to the left and right hand and recordings obtained from the subdural grid placed over the sensorimotor cortex of the right hemisphere. Ipsilateral SEP responses were recorded from stimulation of the right (unaffected) hand, which were smaller in amplitude and longer in latency compared to the contralateral SEP component counterparts. This is in agreement with previous studies in normal humans demonstrating ipsilateral SEP responses in the sensorimotor cortex (such as Yamada et al. 1984; Korvenoja et al. 1995), and with data presented earlier in this thesis (Chapters 7 and 8). As reviewed in Section 6.4.2 of Chapter 6, there are several hypotheses for the presence of ipsilateral SEP responses; volume conduction over the scalp from the contralateral response, the transfer of the contralateral response through the corpus callosum, and a direct projection of uncrossed afferent fibres to the ipsilateral sensorimotor cortex. As an isolated SEP response showed a peak amplitude over the ipsilateral sensorimotor cortex, it is unlikely to be due to spread from the contralateral hemisphere, and is most likely a result of ipsilaterally-projecting afferent fibres present in the patient. In addition, this ipsilateral response was recorded from stimulation of the normal hand to the affected hemisphere, so is unlikely to be present as a consequence of cortical reorganisation.

9.5 Conclusions

Previous studies have shown that the location of sensorimotor and language cortex in the brain is variable in the presence of pathological lesions which produce gross distortions of anatomy. As a consequence, anatomical studies alone may not provide sufficient information to localise eloquent areas of the cortex to allow safe surgical resection of closely related lesions. In this study, fMRI has been demonstrated to be a useful technique in the pre-surgical mapping of the sensorimotor cortex in children. In addition to providing the neurosurgeon with information that can allow planning decisions prior to surgery, fMRI may have a role in potentially avoiding surgery when eloquent cortex is demonstrated to be involved in the lesion, and the risk of a deficit is believed to outweigh the potential benefit of the surgery. This chapter has also described a novel method to localise the subdural grid and intra-operative cortical stimulation positions on an MRI scan of the patient's brain, so allowing a comparison between invasive and non-invasive data. In a number of the cases in this study, the location of the activated region on fMRI was in accordance with cortical stimulation and/or invasive monitoring results. We have found that the combination of fMRI, direct cortical stimulation, and invasive monitoring methods is helpful to the neurosurgeon in the resection of brain masses or epileptogenic tissue located in or adjacent to the eloquent areas of the brain in children. Finally, this study has also demonstrated the use of pre-surgical fMRI in identifying areas of cortical reorganisation of sensorimotor function in children.

Chapter 10: General Discussion

In this study, three techniques (namely fMRI, SEP and behavioural tests) have been used to investigate reorganisation of sensorimotor function in patients following hemispherectomy surgery, in patients with brain infarcts, and in presurgical patients with discrete brain lesions. In this final chapter, the main findings from all three patient populations are considered together. A discussion of the patients involved in the study is given first. This is followed by a discussion of the possible mechanisms of any reorganisation of sensorimotor function, and some of the factors that may have affected brain reorganisation in the patient groups. Finally, some methodological points that have arisen in the study are discussed, and suggestions for further research are given.

10.1 Patient groups

The patients who were involved in this study were all being (or had previously been) treated at Great Ormond Street Hospital for Children, and had suffered brain damage in childhood or in utero. All of the patients who participated in the studies described in Chapters 7 and 8 had to be co-operative enough to undergo behavioural measures or SEP recordings without sedation. The more co-operative patients were also considered for fMRI investigations, a technique which requires a greater amount of patient co-operation than that needed for SEPs investigations or behavioural tests. It is not surprising therefore that the youngest to have SEPs and behavioural tests was 6 years 8 months old (a hemispherectomised patient), whereas the youngest patient who underwent fMRI was 8 years 10 months old (a patient with congenital cortical dysplasia). Therefore the patients participating in this study may not be representative of the population of each patient group as a whole, since it was not possible to study very young or unco-operative patients who would have required sedation to undergo these investigative procedures.

10.2 The reorganisation of sensorimotor function

In this study, ipsilateral sensorimotor fMRI and SEP responses have been demonstrated in patients following hemispherectomy surgery, in patients with brain infarcts, and in presurgical patients with discrete brain lesions. In many of the cases (14 out of 40

* However, it should be noted that as the ipsilateral hemisphere showed fMRI activation on movement of either hand in normal adult controls, the ipsilateral hemisphere may be similarly activated in patients with unilateral brain damage. In other words, in the patients with vascular damage in the MCA territory or with unilateral congenital brain lesions, isolated ipsilateral activation may have occurred due to the suppression of contralateral activation as a result of brain damage, and not necessarily reorganisation of the sensorimotor pathways. In addition, only one out of 14 patients who performed passive hand movement showed isolated ipsilateral primary sensorimotor cortex activation on fMRI (the other showing premotor activation), compared to none of the 10 normal controls. Due to the small number of patients showing this pattern of activation, caution must be exercised when interpreting these data, particularly with respect to any suggestion of functional reorganisation.

patients studied), ipsilateral activation was observed in the absence of activation in the sensorimotor cortex of the contralateral hemisphere. This pattern of ipsilateral sensorimotor responses was seen in ten out of 17 patients following hemispherectomy (Chapter 7), three out of 11 patients with infarcts (Chapter 8), and one patient with a brain tumour (Chapter 9).

Ipsilateral activation also was demonstrated in 5 out of 10 normal controls using fMRI (see Section 6.3.1.1.2 of Chapter 6). There does appear, however, to be a clear distinction between the pattern of brain responses seen in patients with brain disease compared to those in normal controls. In normal controls, ipsilateral fMRI activation was only seen in addition to contralateral sensorimotor cortex activation, showing the involvement of both sensorimotor cortices in subserving unilateral hand function. In contrast, of the patients with brain disease who demonstrated ipsilateral responses, no activation was observed in the contralateral sensorimotor cortex (with the exception of 2 patients with infarcts, as discussed in Chapter 8). In addition, normal subjects showed ipsilateral activation only with an active hand movement task, but not with a passive movement stimulus. In contrast, two patients with brain disease who demonstrated isolated ipsilateral activation did so with a passive hand movement task. It should be noted, however, that the absence of detectable contralateral activation in patients with brain lesions does not necessarily mean that there is no neuronal activity in the appropriate region, since it may be below the level of sensitivity of the investigational techniques used (further discussed in Section 10.3). What can be stated from these findings, however, is that ipsilateral brain function shows greater activity compared to contralateral function in such patients. Collectively, these findings suggest that reorganisation of the sensorimotor system has occurred in a number of patients with brain damage studied in this thesis. ✻

The question arises as to the source of these ipsilateral responses in patients with brain disease and how the ipsilateral sensorimotor cortex becomes more prominent in function compared to normal controls. Ipsilateral sensory and motor pathways, which consist of fibres that do not decussate at the level of the medulla, are known to exist in the normal human, and have been discussed in Chapter 1. Although there is the suggestion that ipsilateral connections are lost during early development (Benecke et al. 1991; Muller et al. 1997a), there is also a wealth of evidence that in fact ipsilateral pathways must also exist in older children and adults (refer to Section 6.4 of Chapter 6). Consistent with this, ipsilateral fMRI activation has been demonstrated in addition to contralateral activation using active hand motor tasks with fMRI in adult volunteers (for example Rao et al. 1993). This finding was also found in this study in a group of normal controls

(reported in Section 6.3.1.1.2 of Chapter 6). However, only a small number of adult controls showed ipsilateral responses, and therefore the even smaller number of children who participated in this study (only one of whom performed an active movement task) possibly explains why ipsilateral activation was not demonstrated in any of the child controls.

The current evidence for the various proposed mechanisms of reorganisation and plasticity of the sensorimotor cortex has been described in Section 1.5 of Chapter 1 and elsewhere throughout the thesis. One explanation for the presence of isolated ipsilateral activations in the reorganised brain (i.e. without visible activation of the contralateral side) is based on the unmasking of ipsilateral pathways. This may be by damage to the sensorimotor cortex of one hemisphere releasing the inhibitory effects on the opposite hemisphere via transcallosal projections (Jeeves & Silver, 1988). Several TMS studies have suggested that ipsilateral responses observed following stroke were the consequence of disinhibition, or unmasking of a normally suppressed or inhibited pathway (Turton et al. 1996; Netz et al. 1997). A second explanation is that novel, aberrant corticospinal pathways may develop following early unilateral central nervous system damage. However, as ipsilateral responses were seen in normal adult controls in the current study, it is unlikely that either of these mechanisms is responsible for the ipsilateral responses observed in patients with brain damage. In particular, it is extremely improbable that the formation of new pathways was the cause of ipsilateral responses in the patients with late-onset acquired disease in the present study.

A further potential mechanism is through the strengthening of such pre-existing ipsilateral pathways (for example Benecke et al. 1991). As mentioned above, ipsilateral sensory and motor pathways have been demonstrated in normal humans (as described in Chapter 1). In the motor system, ipsilateral lateral and ventral corticospinal tracts have been shown to exist (for example Jones et al. 1989). In the somatosensory system, there is evidence for an ipsilateral spinothalamic tract (for example Lyubimov et al. 1980), but the presence of a medial lemniscus tract has not been established. It is thought that ipsilateral neuronal connections may be enhanced or altered as a result of 'forced-use' caused by the loss of the normal contralateral side as the patient uses the hand after the brain damage (Kunkel et al. 1999). From the pattern of reorganisation seen in this present study, and with the demonstration of ipsilateral responses in the normal adult, the strengthening of pre-existing ipsilateral fibres appears the most likely mechanism for inter-hemispheric reorganisation of sensorimotor function in patients with brain damage. The ipsilateral motor cortex activation would occur through the reorganisation of the ipsilateral lateral and/or ventral corticospinal tract. In addition, it is

possible that the ipsilateral spinothalamic tract subserves ipsilateral function; however it is unclear as to the involvement of the ipsilateral medial lemniscal tract. Finally, other pathways including the motor brainstem pathways (such as the ventromedial or rubrospinal pathways) or the somatosensory spinocerebellum pathway may also reorganise to subserve ipsilateral function. As the current literature recognises, the detailed mechanism behind this process appears, as yet, undetermined (for a discussion see Kaas, 1991).

Although some studies have reported homotopic inter-hemispheric reorganisation into primary sensorimotor cortex of the undamaged hemisphere, other studies suggest predominantly non-homotopic (intra-hemispheric) reorganisation (i.e. reallocation of predominant motor functions into secondary motor regions) (Weiller et al. 1993; Cicinelli et al. 1997; Traversa et al. 1997; Seitz et al. 1998). In most studies, such non-homotopic reorganisation has been demonstrated in the sensorimotor systems of the affected hemisphere. Of the cases demonstrating reorganisation of sensorimotor function using fMRI in this thesis, the majority have shown homotopic responses in the ipsilateral primary sensorimotor cortex. A particularly surprising finding in two patients in this study was the increased activation in the secondary sensorimotor areas in the ipsilateral hemisphere, compared to the ipsilateral primary sensorimotor cortex to movement of the affected hand. One hemispherectomised patient demonstrated enhanced ipsilateral activation of the secondary somatosensory area (S-II) in comparison to activation of the primary sensorimotor cortex. Activation in the ipsilateral premotor area was also seen in the same hemispherectomised patient and in one patient with a large cortical infarct affecting the frontal and parietal lobes (Chapters 7 and 8). These data suggest that reorganisation may occur both inter-hemispherically (to the ipsilateral hemisphere) and intra-hemispherically (within the ipsilateral hemisphere) in the same patient. This finding implies not only plasticity of the ipsilateral sensorimotor pathways, but also in the intra-hemispheric connections between the primary and secondary sensorimotor areas of the ipsilateral hemisphere. As with inter-hemispheric reorganisation, the mechanism underlying intra-hemispheric brain reorganisation is also debated (as discussed in Chapters 1, 7, and 8). A network of intra-hemispheric cortical fibres has been shown to exist between the areas of the sensorimotor system (for review see Frackowiak et al. 1997a, 1997b). It is likely that these interconnecting fibres exist in the ipsilateral hemisphere to the affected hand, in addition to the contralateral hemisphere. An alteration in these ipsilateral intra-hemispheric connections may account for the pattern of reorganisation seen in these two patients. For example, as mentioned in Chapter 7, the cortico-reticulospinal pathway has been hypothesised to underlie ipsilateral premotor cortex activation (Benecke et al. 1991; see Section 1.3.4.1 of

Chapter 1). As with a shift to the reliance on ipsilateral fibres described above through the strengthening of pre-existing fibres, so this strengthening of secondary as opposed to primary sensorimotor fibres is likely to have occurred in the ipsilateral hemisphere of these two patients. Intra-hemispheric reorganisation was not seen in any of the patients with discrete brain lesions (Chapter 9). Possibly this pattern of both inter- and intra-hemispheric reorganisation in the same hemisphere may be confined to patients with large cortical lesions, where an extensive amount of, or the entire, sensorimotor system in one hemisphere is affected.

The present study suggests that, in patients with brain damage, inter-hemispheric reorganisation is a more likely mechanism of reorganisation of sensorimotor function than intra-hemispheric reorganisation within the affected hemisphere. This would in turn suggest that the ipsilateral pathway is more 'plastic' than any intra-hemispheric alternatives. This could be a reflection of a number of factors. In the normal controls, ipsilateral sensorimotor cortex activation was more readily observed than activations in the secondary motor areas (refer to Chapter 6; only the SMA was activated in addition to the primary sensorimotor cortex, and this in only a small number of controls). It may be that activity in the ipsilateral sensorimotor pathway results in increased activation compared to secondary sensorimotor areas, and so is more easily detected, both in normal controls and patients with reorganised brain function. The results may also be a reflection of the small number of patients involved in the study.

10.2.1 Factors affecting brain reorganisation and recovery of sensorimotor function

As described in Section 1.5 of Chapter 1, there are many factors which may affect the recovery of sensorimotor function and brain reorganisation. Some of these factors will be considered below, with respect to the findings in this study.

Three groups of patients were involved in this study, each with different extents of brain damage. Hemispherectomy involves the complete disconnection of one entire hemisphere (Chapter 7). In both cases, the entire primary and secondary sensorimotor areas are removed and the hemisphere is disconnected from the remaining side. In contrast, many of the patients with infarcts (Chapter 8) and patients with discrete brain lesions (Chapter 9) did not necessarily suffer from damage to the primary sensorimotor cortex, but instead had insults affecting other parts of the sensorimotor system, for example the basal ganglia, premotor area or supplementary motor area. Several patients, similar to the hemispherectomised patients, had brain damage affecting the whole or a

large portion of the hemisphere, but, as the cortical tissue was still intact, it may still be able to subserve some residual sensorimotor function. This study has thus enabled the comparison of reorganisation of sensorimotor function in patients with different extents of brain damage. A number of studies (for example Chugani et al. 1996) have suggested that patients or animals with large brain lesions, for example involving the entire primary sensorimotor cortex, are more likely to demonstrate reorganisation of the brain to subserve residual sensorimotor function, compared to those with smaller lesions which affect only a specific part of the sensorimotor system. One study in animals found that small neocortical lesions are associated with compensation mediated by brain regions ipsilateral to the side of injury, whereas large lesions trigger compensatory changes in the contralateral hemisphere (Irle, 1987). In other words, with an increase in the size of the lesion, a threshold is reached whereby there is a switch from intra- to inter-hemispheric reorganisation. The results of the present study, however, did not show this pattern; patients with smaller brain lesions, such as tumours or cortical infarcts in the vicinity of the sensorimotor area, appear as likely to show inter-hemispheric reorganisation as patients with large brain lesions affecting the whole hemisphere. The results also suggest that patients who suffer subcortical damage to sensorimotor areas such as the basal ganglia may also demonstrate cortical reorganisation through ipsilateral connections (Chapter 8). In contrast, the extent of residual sensorimotor function in the affected hand differed widely between the patient groups. As expected from the previous literature, hemispherectomy surgery (in addition to the original brain damage) had a severe effect on the contralesional sensory and motor function of the upper limb in all the patients studied, compared to only a few patients rendered with little or no motor and sensory function following brain infarcts (compare the residual sensorimotor function in the affected hand of patients in Chapters 7 and 8). Patients with infarcts generally had a better recovery of sensorimotor function than hemispherectomised patients.

There was great variability in the age of onset of brain damage in the children investigated in this study. The hemispherectomised patients had their initial brain insult either congenitally or in childhood (Chapter 7). In patients who suffered infarcts in childhood, the insult also occurred at very different ages (and as a comparison two patients in the study had congenital disease, see Chapter 8). Finally, the patients who underwent brain functional mapping studies presurgically had also suffered brain damage at different ages, either congenitally or as children (Chapter 9). There was no apparent relationship between the age of brain damage and the demonstration of brain reorganisation. It appears that the patients with brain lesions sustained late in life were as likely to demonstrate reorganisation of sensorimotor function as those with early lesions. This is contradictory to many previous studies carried out in children and

animals, which have suggested that the earlier the brain damage, the more likely reorganisation of the brain is to occur (for example Muller et al. 1997b); see Section 1.5 of Chapter 1). One explanation for the apparent discrepancy is that almost all of the brain lesions in the children studied in this thesis were acquired before cortical maturation was complete (34 out of 40 patients). Muller et al. (1997a) demonstrated the presence of ipsilateral MEP responses in normal children up to the age of 10 years, after which no ipsilateral MEPs were observed. Of the patients who showed ipsilateral responses with fMRI or SEPs, (10 hemispherectomised patients, 5 patients with infarcts, and one presurgical patient), all except one (a patient who suffered an infarct at 15 years of age) had suffered brain damage at 10 years of age or younger. The implication is that the majority of patients were young enough at the time of brain damage to have a functioning ipsilateral sensorimotor pathway. This pathway may have maintained function even after 10 years of age due to strengthening in response to damage to the contralateral sensorimotor system (see Section 10.2). Another explanation for the absence of a relationship between the age of brain damage and the demonstration of brain reorganisation is that only a relatively small number of patients were investigated in the whole study (40 patients in total). As described above, the patients involved may not be representative of each of the patient populations as a whole. In addition, the patients differed widely with respect to other influencing factors, such as duration of epilepsy and extent of brain damage. This considerable variability of clinical history across patients makes it difficult to treat them as distinct groups. The patient groups would need to be increased in number if these other factors were to be controlled for.

The extent of residual sensorimotor function was dependant on the age at injury in the hemispherectomised patients. Patients with congenital disease who had undergone a hemispherectomy had better residual sensorimotor function than hemispherectomised patients with acquired disease. However, there was no clear relationship between the age at onset of brain damage and the extent of residual sensorimotor function in patients with infarcts or discrete brain lesions. It is likely in these latter two groups of patients, however, that the extent of residual sensorimotor function is dependent not only on the timing of brain damage, but more importantly on the site of brain damage, which is clearly variable and in most cases less extensive than for the hemispherectomised patients.

Another factor which may influence the extent of residual sensorimotor function and brain reorganisation in these groups of patients is the period of seizure activity (Vargha-Khadem et al. 1994; Beckung et al. 1994, see Section 7.1.5. of Chapter 7). Any brain damage which results in epilepsy is also likely to result in physiological and anatomical

changes in the intact brain structures surrounding the abnormal tissue. In the present study, the length of time during which patients experienced epileptic seizures varied between 4 months and 8 years for patients who had undergone hemispherectomy, and from less than 1 month to 14 years in patients with discrete brain lesions. Despite the reasonably large difference in the duration of epilepsy, there was no obvious relationship seen between the duration of epilepsy and the brain reorganisation in hemispherectomised patients or patients with discrete brain lesions (Chapters 7 and 9). In addition, no relationship was observed between the duration of epilepsy and the residual sensorimotor function in the affected hand of the patient.

In patients who had undergone hemispherectomy surgery and in patients with infarcts, there was no significant association between evidence of brain reorganisation and the extent of residual sensorimotor function (Chapters 7 and 8). Hemispherectomised patients with residual function, by the nature of brain damage, must reorganise sensorimotor function to either the ipsilateral (remaining) hemisphere, or to the subcortical (unresected) structures. In the present study, patients with good residual motor and/or sensory function did not necessarily show ipsilateral fMRI or SEP responses. In fact, of the two patients who demonstrated ipsilateral sensorimotor responses, neither had residual motor function and both had a mild to severe sensory deficit. In contrast, patients with infarcts may not need to reorganise sensorimotor cortical tissue in order to maintain contralateral residual sensorimotor function, particularly if the infarct does not directly affect the primary sensorimotor area. However in this study, ipsilateral sensorimotor responses were demonstrated in patients who did not have complete recovery of sensory and/or motor function, even when the infarct did not directly affect the primary sensorimotor cortex. This finding of no correlation between the extent of residual function and the presence of reorganisation is consistent previous literature in patients following brain damage (for example Netz et al. 1997). At present, there does not appear to be a clear explanation for these data. It is clear that more studies are needed in patients with different extents of residual function following brain damage to determine the involvement of the ipsilateral sensorimotor cortex in functional recovery.

10.3 Methodological Considerations

To my knowledge, this is the first study reported to combine SEP, fMRI and behavioural investigations of sensorimotor function following brain damage. A small

number of studies have previously used a combination of other techniques to investigate functional sensorimotor recovery in patients who have suffered brain damage to the sensorimotor system (for example Rossini et al. 1998; Seitz et al. 1998; Hernandez et al. 1999). The combination of different methods of functional brain imaging in the same subjects allows complementary information on the sensorimotor system to be obtained. In particular, methods to investigate brain function differ widely in temporal and spatial resolution; for example fMRI offers excellent spatial resolution, and SEP recordings excellent temporal resolution. The present study has demonstrated, using SEP and fMRI measures, reorganisation of the sensorimotor systems through the recruitment of ipsilateral pathways in a number of patients with brain damage. Despite the various activation modalities of the different techniques employed in this study, it is still of interest to observe a similar inter-hemispheric shift of the sensorimotor hand areas to the unaffected hemisphere with the two techniques. With ongoing advances in methodology, other multimodal studies carried out to evaluate brain function (such as those including TMS and PET) may also be of significant help in studying patients with brain lesions. In future studies, it would be of interest to use such methods (which rely on different activation modalities to those used in this study) in patients following hemispherectomy and stroke to confirm the findings in the present study.

A surprising finding in this study was the inconsistency between the numbers of patients demonstrating brain plasticity of the sensorimotor cortex using fMRI and SEP methods in two of the patient groups. In the group of hemispherectomy patients, ipsilateral SEPs were more readily detected than ipsilateral fMRI activation (Chapter 7). In contrast, the stroke patient group showed ipsilateral fMRI activation more frequently than ipsilateral SEPs (Chapter 8). The reason for this discrepancy is unclear. However the finding highlights an advantage of using a number of different techniques that use different stimuli to activate the sensorimotor system to examine normal and abnormal brain function. fMRI activation using passive or active movement is likely to involve a greater motor component than SEP responses evoked by electrical or vibration sensory stimuli applied to the hand. In addition, whereas fMRI locates activated brain regions through haemoglobin oxygenation changes in the blood (a secondary response), SEPs detect more directly the cortical response in the brain through focal electrical activity. The reorganised functional pathways in the different patient groups are clearly more sensitive to one technique than the other; however, it is unclear at present if this is a reflection of the different brain lesions or of the individual patients themselves.

The issue of sensitivity of the techniques used in the study may affect the results in other ways. For example, as mentioned above, it may have influenced the undetermined

relationship between brain reorganisation and the extent of residual sensorimotor function in two of the patient groups investigated in this study. A large variation in the significance of activated regions using fMRI has been seen within volunteer datasets (for example see Chapters 3 and 6). In a reproducibility study reported in Section 3.5 of Chapter 3, each of the volunteers showed variable percentage signal changes of cortical activation to a sensorimotor task, both within a fMRI session and between sessions. Within a volunteer, the percentage signal change was seen to vary over approximately 2-3% (about a mean of 2.4%; see Figure 3.14 of Chapter 3). It is likely that this phenomenon also occurs in the patients being investigated in this study. It is possible that of the patients who did not show reorganisation of brain function, the level of activation was below the sensitivity of the fMRI technique for that particular examination. In other examinations, ipsilateral sensorimotor responses may have been detectable if the activation was above the sensitivity threshold for that fMRI experiment. This phenomenon highlights the importance of repeating experiments to confirm results in patient as well as normal controls. However it is more difficult to repeat studies on patients, particularly when they have a large distance to travel and/or are less co-operative in lying in the scanner for a long period of time. Therefore, it is conceivable that in the patients with good residual function, the neuronal activity that must be present to subserve the function is undetectable using the methods employed.

In addition to the more commonly used electrical SEP technique for assessing sensorimotor function, vibrational SEPs were also carried out in this study. As described in Chapter 4, vibration has the advantage over electrical stimulation methods of being a less painful stimulus and so more suitable for children (see for example Hyvarinen et al. 1980). To my knowledge, this is the first study using vibrational SEPs, in addition to electrical SEPs, to investigate reorganisation of sensorimotor function in children with brain damage. Data collected in patients following hemispherectomy and brain infarcts demonstrated not only normal contralateral SEPs on stimulation of the unaffected side, but, in a small number of patients, ipsilateral SEPs on stimulation of the affected side. Ipsilateral SEPs recorded in these patients were inconsistent between the two types of stimuli. In a number of hemispherectomy cases, ipsilateral vibrational SEPs were only recorded in patients who also demonstrated ipsilateral electrical SEPs; however not all patients who showed ipsilateral electrical SEPs demonstrated vibrational SEPs (Chapter 7). In this group of patients it appeared that electrical SEPs were more likely to show reorganisation of sensorimotor function than vibrational SEPs. In contrast, only one patient with a brain infarct and one patient with congenital cortical dysplasia demonstrated ipsilateral electrical or vibrational SEPs (Chapter 8). More prevalent in this group of patients was the absence of one or all of the

contralateral components of the electrical or vibrational SEPs. In particular, the contralateral N60 component was absent in the vibrational SEP in a number of patients with brain infarcts. One explanation for the discrepancies between the two patient groups (in addition to the differences in the two techniques described above) is the difference in the extent of the brain lesions. Hemispherectomised patients function entirely on a single hemisphere, so any cortical SEP responses must originate from the remaining hemisphere. Many of the patients reported in Chapter 8, however, only suffered from focal cortical or subcortical damage, which may affect only a specific fibre type or SEP generator. The differences between ipsilateral responses detected following electrical and vibration stimuli must be attributed to the stimulus type. Electrical stimuli activate the median nerve directly via the stimulus applied on the wrist overlying the nerve, whereas vibration is a mechanical stimulus applied to the surface of the skin at the fingertips. As shown in Chapter 4, vibrational SEP components are smaller in amplitude and longer in latency than the electrical SEP counterparts in normal controls. The difference in the sensitivities of the two responses shown in Chapter 4 may explain why ipsilateral electrical SEPs are more readily detected than ipsilateral vibrational SEPs in the hemispherectomised patients.

Consideration must be given to the possibility that the hemisphere without a lesion may not be entirely normal in patients with brain damage, despite the presence of a single localised and lateralised lesion (also suggested by Weiller et al. 1992). Ipsilateral sensory and motor deficits have been reported in patients following hemispherectomy in a number of studies (for example Cairns & Davidson, 1951; Muller et al. 1991). Careful clinical examination of previously healthy patients who have suffered a stroke affecting one cerebral hemisphere may reveal mild weakness and impairment of fine motor skills in the 'unaffected', ipsilateral, arm (for example Colebatch & Gandevia, 1989; Jones et al. 1989). Indeed several studies have suggested that cerebral infarcts may have remote effects on the ipsilateral cortical CBF circulation (Meyer et al. 1979; Takano et al. 1985). In detailed self observations following his own stroke which resulted in a left hemiplegia, Brodal, (1973) described problems with writing and other skilled tasks using the right hand, suggesting that the lesion which in this case was in the right cerebral hemisphere had damaged pathways which normally contribute to control of some movements of the ipsilateral upper extremity. However, the motor deficits in the limbs ipsilateral to the infarcted hemisphere appear to be very mild in most cases (Dijkerman, 1996). In this study, there was no obvious difference seen between the contralateral SEP, fMRI and behavioural responses from the unaffected hand in patients with brain disease, compared to the responses observed in normal control subjects. However, even in the event that the 'unaffected' hand may not be entirely normal in

function, all of the incidences of ipsilateral responses from the affected hand in this study are very obviously unlike the pattern of brain activity seen in any of the normal controls.

10.4 Future Studies

Several areas of the work described in this thesis require further investigation in future studies. It would be important to further delineate the mechanisms of functional sensorimotor organisation in the groups of patients investigated in the present study. At present, this can only be done by more direct physiological investigations, which can be performed most rigorously in monkeys and other animals. It is hoped that advances in comparative anatomy and physiology between different primates, including humans, will allow us to combine our knowledge about functional changes in the brain with more fundamental knowledge about their mechanisms. In particular, future studies must address the issue of inter-hemispheric versus intra-hemispheric reorganisation of the brain, and which of these mechanisms is most prevalent in a large group of patients with brain damage. Further knowledge about the connectivities between brain areas in these patients may allow us to identify the site of the functional activation not only as a separate location of neuronal activity but also as a part of a functional network of motor areas that are involved in brain reorganisation and residual sensorimotor function.

Relatively little is known about the differences in functional organisation underlying mild versus more severe somatosensory and motor deficits. Although the patients examined in the present study included those with a range of residual sensory and motor function in the affected hand, no relationship was observed between the demonstration of reorganisation of brain function and the extent of residual sensory of motor function. It would therefore be of further interest to continue the study to include a greater number of patients that may be more representative of the patient population as a whole. Future studies should not only continue to investigate the relationship between functional reorganisation and the extent of residual function, but also other factors that may influence them. The findings of the current study suggest that, in patients who suffer a brain lesion early in life, the developmental stage at the time of the brain lesion may not be as important a factor in brain reorganisation as had been previously anticipated. However, the timing of the brain lesion does appear to affect the extent of residual sensorimotor function. Previous human and animal lesion studies have found both factors to be strongly influenced by the timing of brain damage (refer to Section 1.5 of Chapter 1). There are other variables that may influence residual sensorimotor function

and brain reorganisation, most of which have not been possible to investigate in this study. These include the duration of epilepsy, severity and type of epilepsy, medication type and level, aetiology, environmental variables, and integrity of the remaining brain structures (for review see Chugani et al. 1996). For example, Vargha-Khadem & Polkey (1992) pointed out that a long standing disease process that precedes hemispherectomy surgery may affect the functional organisation of not only one but both hemispheres. In the studies described in Chapter 7, it may be that the remaining hemisphere in patients with ipsilateral activation was less affected by seizure activity and anticonvulsant medication than the remaining hemisphere in patients who did not demonstrate brain reorganisation. This suggestion, however, must remain speculative as the number of subjects was small and the subjects differed on several other potentially relevant variables, such as aetiology and severity of seizures. It would be of interest to investigate in future studies what influence this factor, and other factors, have on the potential for functional reorganisation after brain damage and on the recovery of sensorimotor function. Considering the small number of children having either hemispherectomy surgery, infarcts affecting the middle cerebral artery territory, or tumours/brain lesions in or around the primary sensorimotor cortex, in addition to the complexity and individualism of each patient, there are considerable (perhaps insurmountable) practical problems to overcome to obtain such information.

As mentioned above, investigations in patients with brain damage may not only hold considerable promise in understanding the mechanisms of cortical reorganisation, but also provide insights into how to manipulate these systems to promote recovery from disease and injury or to overcome somatosensory and motor dysfunction (for example Stein & Glasier, 1992). In the future, this knowledge may indicate how such mechanisms can be modulated either pharmacologically or by physiotherapy to lead to a better outcome for patients. There are several areas of research which should be further investigated. Firstly, serial fMRI and SEP studies which commence before the completion of stroke recovery will shed greater light on the specificity of altered brain activation for neurological recovery. Following the pattern of brain reorganisation days, weeks, or even months after the insult using fMRI will provide a greater understanding of which mechanism of reorganisation is most prevalent during recovery, and at which stage in the process. In addition, it would be interesting to perform serial fMRI and SEP studies in patients recovering from different brain lesions (for example hemispherectomy or stroke), to determine whether patients with different extents and timing of brain damage follow similar patterns of brain reorganisation.

Secondly, in contrast to the extensive research with functional imaging or electrophysiological mapping dealing with spontaneous recovery and cortical reorganisation after stroke, surprisingly little research has been directed towards behavioural aspects of motor recovery or the intriguing question of to what extent physiotherapy and other external stimuli applied during rehabilitation can enhance or speed up functional recovery. This topic of rehabilitation is of interest in the present study for further understanding functional sensorimotor recovery. A number of primate and human studies have suggested that sensorimotor experience after injury to the motor cortex plays a major role in the subsequent physiological reorganisation (for example Pascual Leone et al. 1994; Karni et al. 1995; Nudo et al. 1996). It is possible that functional reorganisation in the primary and/or associated motor cortices underlies the improvement in motor function seen in patients undergoing similar rehabilitation therapy following damage to the sensory or motor system. Indeed, Nudo and his colleagues (Nudo et al. 1996) demonstrated that in the absence of post-injury rehabilitative therapy, the tissue surrounding the focal infarct undergoes a further territorial loss in the functional representation of the affected body part. It is unclear at present if this is due to learned non-use or to a disruption of local (intrinsic) cortical circuitry. Many therapeutic approaches are currently available in humans (see for example Aisen et al. 1997; Feys et al. 1998; Nelles et al. 1999); however considerable controversy exists about their effectiveness. In addition to standard intensive physiotherapy post-injury, two techniques have received particular attention and have been shown to provide a significant improvement to residual limb function. An improvement in motor performance in stroke patients has been successfully influenced by sensoric stimulation of afferent pathways (using whole hand electrical stimulation with a mesh glove) (Dimitrijevic et al. 1996; Golaszewski et al. 1997; Hummelsheim et al. 1997). The other form of therapy involves constraining the upper extremity of the unaffected limb which has been shown to result in long-term improvement of motor function in the impaired limb (known as constraint-induced movement therapy) (Taub et al. 1993; Liepert et al. 1998). The results of these latter studies, in conjunction with research on cortical reorganisation in adult phantom limb patients (Flor et al. 1995), suggest that the size of the cortical representation of a body part in adult humans depends on the amount of use of that part. The inclusion of these and other additional rehabilitation techniques alongside the current methods may elevate the potential for functional sensorimotor recovery. With the use of brain mapping techniques such as fMRI and SEPs, it would be interesting to examine brain reorganisation alongside rehabilitative functional recovery. Comparing the pattern of brain functional activity and motor or sensory recovery with and without rehabilitation may help us to understand the temporal mechanisms of brain reorganisation and the possible functional benefits of rehabilitation.

10.5 Summary of Conclusions

The main findings of this study were as follows:

- Reorganisation of brain function was demonstrated in children with brain damage.
- Brain reorganisation can occur both inter-hemispherically (through the enhancement of pre-existing ipsilateral pathways) and intra-hemispherically (with increased activity in the secondary compared to primary sensorimotor areas in the ipsilateral hemisphere) in the same patient.
- Brain reorganisation does not appear to be associated with the extent of residual sensorimotor function, irrespective of type or extent of brain damage.
- No relationship has been demonstrated between the timing of the brain insult and brain sensorimotor reorganisation.

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