DYNAMICS OF TRANSIENT AND STEADY-STATE RESPONSES EVOKED BY MECHANICAL STIMULATION OF THE DIGITS

By

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Abstract

The basic problem addressed by the experiments of this thesis was how the human brain organizes the information transduced by the receptors of the somatosensory system (*somatotopic maps*), and how representations of that information are updated as a consequence of sensory experience (*plasticity*). The experiments of this thesis were designed to measure somatotopic maps of the digits in adult human subjects (experiment 1 & 2) and to measure the reorganization of these representations following discrimination training (experiment 3).

Experiment 1 of this thesis confirmed that somatotopic representations evoked by 1.5 Hz mechanical stimulation of the digits can be measured noninvasively by applying dipole analysis to EEG and MEG field patterns. Source localized responses from EEG and MEG projected onto a region of postcentral gyrus and were in agreement with known anatomical landmarks near somatosensory area 3b. This experiment was the first to provide evidence of digit somatotopy by recording EEG responses to mechanical digit stimulation. However, the procedures used to map somatotopic representations were impracticably long (>5 minutes per digit), prompting the development of more efficient steady-state stimulus procedures investigated in experiment 2.

Experiment 2 compared somatotopic maps of the digits derived from the presentation of a 3 Hz "transient" stimulus with that of an 18 Hz "steady-state" stimulus. Results from this experiment showed that somatotopic maps observed using a steady-state stimulus were remarkably similar to those observed using a transient stimulus and both maps were observed to be stable over repeated measurements. However, the

steady-state maps were obtained in half the measurement time. The results from this experiment demonstrate that steady-state stimuli may be a more efficient procedure for mapping somatosensory representations.

Experiment 3 used steady-state stimulation to investigate whether somatotopic representations are statically fixed or whether they can be remodeled by temporally coherent stimulation during a tactile discrimination task. In this experiment, subjects were trained for three days to detect changes in the frequency of a 21Hz tactile stimulus applied to digits 2 + 3 + 4 (fusion condition) or 2 + 4 (segregation condition) of the right hand. Results from this experiment showed changes in the 21 Hz representation for digit 3 were obtained on the third day of training for a subset of subjects in the fusion condition and for the segregation group as a whole.

The results from this thesis build upon a body of research which employs noninvasive procedures to describe the organization of the human somatosensory cortex. These noninvasive measurements help to extend our basic understanding of how the body represents somatosensory stimuli in the brain. Further, this thesis adds to a growing literature which demonstrates that the adult somatosensory cortex is capable of reorganization, depending both on the pattern of peripheral stimulus and the adaptive relevance of the stimulus to the individual.

Preface

This thesis is comprised of two papers (chapters 3 and 5) that are published in Brain Topography Today and Neuroreport, respectively. Chapter 2 was a collaborative effort between myself, Drs D. Cheyne, L.E. Roberts, and D. Bosnyak. I was involved extensively in all aspects of this work, including design and construction of the stimulus and collection of pilot data, data collection and analysis, and preparing the manuscript for publication. Chapter 4 was a collaborative effort between myself, Li Chan Liu, D. Bosnyak and L.E. Roberts. I was involved extensively in formulating the experiments, collecting the data, analyzing the data, and preparing the manuscript for publication.

Acknowledgements

I would like to acknowledge the support and supervision of Dr. L.E. Roberts. Dr. Roberts has supervised by example – by holding himself to the highest standards of scholarship and scientific research. This thesis and I profited enormously from his influence.

Dan Bosnyak deserves high praise for helping me get several of my experiments off the ground. Dan's technical skill and keen scientific mind made him an ideal collaborator and fellow lab partner. While I can attribute much of my own scientific development to our time shared together, it is our friendship that I value even more.

I was also very fortunate to work with Doug Cheyne on several experiments over the course of this thesis. Our collaborations have been extremely rewarding and enjoyable for me. Doug exhibits a rare and enviable combination of scientific capability and joie de vivre.

Finally, and most importantly, I acknowledge my wife Leah. Without her support, patience and optimism, I may never have made it this far.

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Chapter 1

General Introduction

Take a look, literally, at the physical world around you at this very instant. As you explore the environment, detailed information about the features of objects is conveyed to your brain by its sensory systems including vision, hearing, and the skin senses. The basic problem addressed by the experiments of this thesis is to understand how the human brain organizes the information transduced by the sensory receptors, and how representations of that information are updated as a consequence of sensory experience. If our brains did not have the capability to represent our dynamic sensory worlds, we would be unable to carry out even the simplest adaptive act.

Somatopic Maps

One mechanism used by the brain to represent its sensory world is the *sensory map.* If an object is touched with a single fingertip, detailed information about that object (for example, its shape and texture, whether it is moving, and its temperature) is transduced by specialized receptors in the skin and conveyed to a group of neurons or "cortical column" in area 3b of somatosensory cortex, located on the posterior bank of the Rolandic fissure in the contralateral hemisphere of the brain. If the object is then touched with an adjacent finger, parallel information is conveyed to an adjoining cortical column of neurons in area 3b, and likewise for other fingers that may be receiving somatosensory stimulation during manipulative tactile behavior. This cortical organization, in which adjacent surfaces of the skin are represented by adjacent columns of neurons in the somatosensory cortex, constitutes a "somatotopic" map of the hand area. Other body surfaces are similarly represented in adjoining regions of the somatosensory cortex, including most prominently the region of the face, feet, genitalia, and hand area, and the spatial ordering of these areas in the cortex is broadly consistent

between different individuals. Sensory maps are a general principle of sensory organization and are found in other sensory modalities (for example, the tonotopic maps of auditory cortex, or maps in the visual cortex for ocular source, retinotopic location, and spatial frequency content), although the specific nature of these maps varies with the type of information transduced by the sensory receptors. The experiments of this thesis were undertaken to investigate the somatotopic organization of the human hand area. However, the questions that are asked and the methods developed to investigate them may be applicable to other sensory systems as well.

Penfield and Boldrey (1937) first described somatotopic maps of the human body surface. In their pioneering studies, small electrical currents were applied to the exposed cortex of conscious patients undergoing surgery to control epileptic seizures. Body movements and tactile sensations reported by the patients were used to identify which cortical sites processed information from particular regions of the body. The results are summarized by the somatosensory homunculus depicted in Figure 1 which is commonly reproduced in most introductory textbooks of neurology and neuroscience. Figure 1 shows a coronal section of the brain where

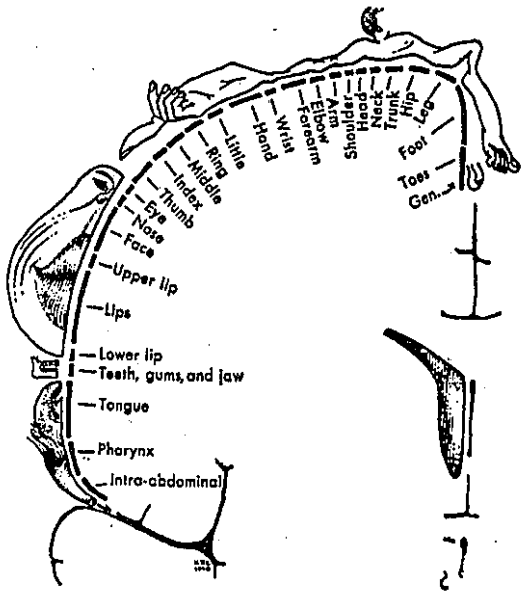

Fig. 1. Penfield's famous *somatotosensory homunculus* which illustrates the relative contribution of skin senses mapped onto somatosensory cortex. Size of the body part on the midline coronal section is roughly proportionate to the density of peripheral nerve fibers. From Penfield and Rasmussen, 1950.

the genital and foot representation appears most medially toward the midline of the brain, followed by increasingly lateral and inferior representations of the leg, trunk, arm, hand, face, teeth, tongue and pharnyx. Each body part is represented in the brain proportionate to its relative importance to sensory perception. For example, the tongue representation is relatively large compared to the arm or body trunk. These representations are organized contralaterally, with the left side of the body represented on the right somatosensory cortex and the right side of the body represented on the left somatosensory cortex. Between the arm representation and the face representation is the hand area. Within the hand area, the representation of the little finger is medial and superior than that of the thumb, with intermediate digits arching between these sites in a medial to lateral plane (see Figure 1).

Somatotopic maps of the hand area were studied in more detail by Michael Merzenich, Jon Kaas and their colleagues in a series of experiments commencing in the 1970s. In these experiments, microelectrodes were inserted into several regions of the somatosensory cortex of anesthetized owl monkeys, including Brodmann areas 3a and 3b as well as the adjoining Brodmann areas 1 and 2 posterior to these zones. Recordings were taken of neural responses to tactile stimulation of the non-hairy surface of the hand. The results are summarized in Figure 2 (from Kandel, Schwartz, and Jessel, 1992). Figure 2 shows that each subregion of the primary somatosensory cortex (areas 3a, 3b, 1 and 2) has its own complete representations of the body surface. Panel A shows somatosensory maps in areas 3b and 1 in a dorsolateral view of the brain of an owl monkey. Panel B shows a more detailed illustration of the glabrous (hairless) pads of the palm and digits in areas 3b and 1. Insert 2b shows an idealized map of the hands based

on a large population of monkeys. Here, the distorted representations of the palm and digits represent the extent of enervation of each hand area in the cortex. Subsequent studies of old world monkeys revealed somatotopic arrangements of the hand area in several regions of the postcentral gyrus in primary somatosensory cortex (SI), as well the upper bank of the Sylvian fissure (SII) and the posterior parietal cortex (Merzenich et al., 1978; Kaas et al., 1979).

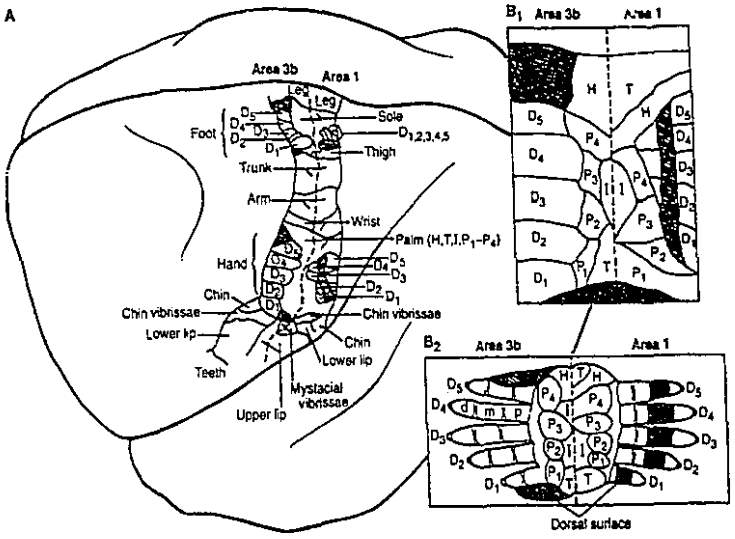

Fig. 2. Panel A shows owl monkey somatosensory representations in areas 3b and 1 for the hand and foot (numbered D1 to D5). Panel B1 shows the representation of the glabrous pads of the palm in areas 3b and 1 in greater detail. Panel B2 shows an idealized map of the hands based on a large sample of monkeys. The palm and digits representations reflect the extent of innervation of each palmer area (thenar (T), hypothenar (H) palmer (P) and insular (I)) in the cortex. The dorsal hand surface is shaded (from Kass et al., 1983).

Noninvasive Measurement of Somatotopy in Humans

Until recently, most of our knowledge about somatotopic representations was derived from invasive studies such as those of Merzenich and Kass which used acute anesthetized animal preparations. These studies have provided a great deal of information about the structure of maps for different properties of somatosensory stimulation and about the flow of information processing in the somatosensory cortical projection pathways. Within the last ten years it has become possible to measure somatotopic representations in the human brain non-invasively, using techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and the

magnetic counterpart to EEG, magnetoencephalography or neuromagnetometry (MEG). These studies have been motivated by two goals. First, noninvasive measurements in humans allow comparison with animal data. Second, because normal human subjects as well as patient populations can readily be investigated over a wide range of conditions, the number and type of questions that can be asked expand considerably. Of special interest have been studies that investigate the temporal dynamics of somatosensory representations. Growing evidence indicates that somatosensory representations are not statically fixed, but are adjusted by context and experience to represent the pattern of stimulation experienced on a task. Study of temporal dynamics on brief time scales requires highly efficient methods of imaging which are stable and offer acceptable temporal and spatial resolution.

Several researchers have recently used EEG or MEG to non-invasively map somatosensory digits representations in humans (Buchner et al., 1995; Baumgartner et al., 1991b; Suk et al., 1991; Raichle, 1994). In this approach, the electrical or magnetic field evoked by tactile stimulation is modeled by one or more "equivalent current dipoles" (ECDs) that may be co-registered on individual neuroanatomy measured by MRI. ECD analysis shows the location, orientation, and strength of the neural "generator" of the scalp recorded EEG or MEG. Specific waveforms may be selected and modeled by ECDs that represent the hand area. For example, the uppermost panel of Figure 3 shows the evoked response to tactile stimulation of the thumb. Stimulation evokes an observed pattern over the scalp with anterior electrodes negative and posterior electrodes positive at 50 milliseconds (called the *P50* response; see Figure 3). This pattern could be produced by depolarization of cortical columns in somatosensory area 3b. This

activation can be modeled by placing a theoretical current source (a dipole) in a sphere representing the head using computer software. Depending on the position, orientation and strength of the dipole, a topographic pattern can be calculated and compared to the observed pattern. The dipole's position, orientation and strength are adjusted iteratively to reduce the difference between the observed and calculated fields. The ECD model is *accepted* when the disparity between the observed and calculated topographies is minimized. Following dipole analysis, acceptable dipole solutions are often co-registered onto the subject's MRI. This co-registration procedure helps to validate the dipole solution by examining the brain areas where the dipoles reside.

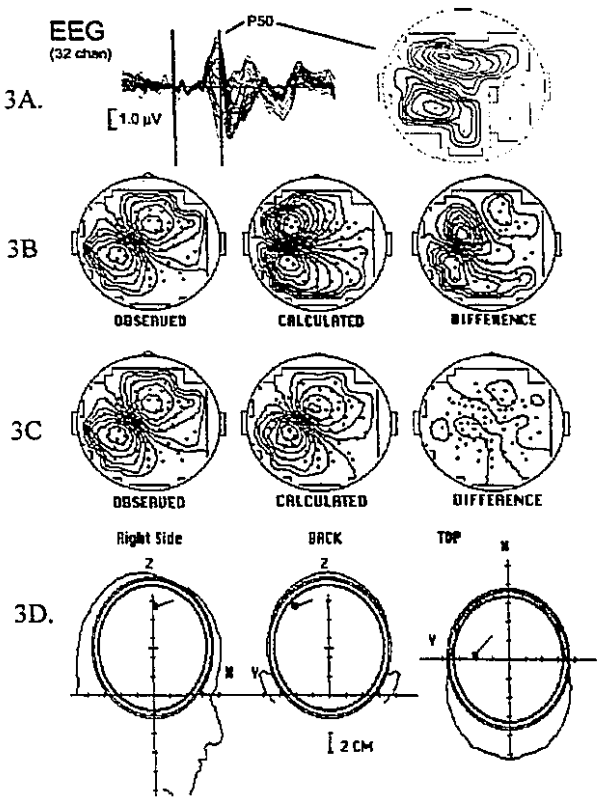

Fig. 3. Panel 3A shows the EEG response to 3 Hz mechanical stimulation of the thumb. The overlay of all electrodes is shown with a horizontal line marking the P50 response. The P50 topography is shown to the right. Panel 3B shows the topography of the observed field compared to the topography of a dipole placed in the area of somatosensory cortex. Note the large amount of residual difference. Panel 3C shows the calculated field after iterations (< 5% residual variance). Panel 4D shows the dipole location and orientation calculated in panel 3C.

Many MEG/EEG mapping studies (Buchner et al., 1995; Kristieva-Feige et al., 1997) have used electrical stimuli which co-activate several receptor types, each of which conveys different information to the brain. Studies employing mechanical stimuli (which may activate receptor populations more selectively) are fewer in number, and have used

MEG to investigate somatotopy (e.g., Suk et al., 1991; Yang et al., 1993; Mogilner et al., 1993). Study of somatotopy with mechanical stimuli and EEG (a more widely available technique than MEG) has only recently been reported (Braun et al., 2000). The question of using mechanical stimulation to observe somatotopy with EEG was therefore a central question of this thesis. Mechanical stimuli were used in this thesis to observe somatotopy, determine the repeatability of maps and to optimize measurement procedures. Finally, the mechanical stimulus was used to determine whether changes to the observed somatotopic representations could be induced by experience with patterned somatosensory stimulation. The study of inducing such changes in functional cortical organization is generally referred to as *cortical neuronal plasticity,* which I introduce briefly in the next section.

Plasticity of Somatosensory Representations

The preceding paragraphs have introduced the functional organization and measurement of the human somatosensory system. It has been long understood that these functional representations are dependent on sensory experience during early development. For example, if a kitten's eye is deprived input from birth, ocular dominance columns for that eye will fail to develop. Until recently, the neural organization established by early experience was thought to be hard-wired in adults, and resistant to modification thereafter. This view has been called into question by evidence from important animal studies showing that the *receptive field* of a neuron, which is defined as the peripheral stimulus to which a neuron responds, can be altered in adult subjects. The results from these experiments inspired the new field of cortical neuronal plasticity.

Cortical neuronal plasticity can be defined as the relatively permanent shift in the receptive field of a cortical neuron to a new receptive field that may be larger or smaller or be associated with a different body part (Dykes, 1997). Changes in receptive fields have commonly been observed by removing an input to the cortex (deafferentation). Well-known examples of somatosensory cortical plasticity have been brought about by nerve transection and amputation in the monkey, raccoon, and the cat (see Dykes 1997 for a review). In these experiments, new and relatively large receptive fields have been observed on nearby skin surfaces only hours or even minutes after deafferentation procedures. Changes occurring this quickly are generally thought to occur when neurons in the deafferented region fail to distribute surround (lateral) inhibition to their neighbors, with the result that these neurons begin to respond to input via lateral connections from these neighbors thus reflecting a new tuning preference.

An alternative but comparable approach to demonstrate the plastic nature of the somatosensory cortex is by the implementation of learning paradigms. Jenkins et al. (1990) showed that when a monkey repeatedly used two digits to make a tactile discrimination to receive a fruit juice reward, the area of the cortical representation for those digits increases. Jenkins et al. (1990) observed that neurons previously unresponsive to the training stimulus appeared following tactile discrimination learning. Later, Recanzone et al. (1992) showed that these changes were sensitive to the animals attention and participation. Unlike changes induced by deafferentation, which may be produced by several mechanisms including release from surround inhibition, changes induced by behavioural training are believed to be due to increases and decreases in synaptic efficacy taking place in the cortical and subcortical layers via Hebbian

mechanisms (neuroplasticity). While there is ample evidence that the somatosensory system is capable of neuroplastic modification in the adult mammalian brain, evidence that such changes can be observed non-invasively in humans has only recently been observed.

The Central Questions of the Thesis

The adult human brain is organized in an orderly and meaningful way. The processes that maintain this order and the conditions that allow reorganization to occur are central to our understanding of how the human brain works. In order to learn more about these basic processes, this thesis investigates non-invasive methods for measuring somatotopic representations in the intact human subject, and the application of these methods to the study of plasticity in the adult human brain. The central questions of this thesis are: can we map somatosensory cortex with high resolution EEG? Furthermore, are there procedures that would allow for a more efficient mapping of somatosensory cortex using EEG? And finally, can we induce and measure changes in the somatosensory system non-invasively in normal adult human subjects?

The thesis is organized in the following way. Chapter 2 reviews the anatomical details of the somatosensory pathway, describes "somatosensory evoked potentials" (SEPs) and how they can be used to measure somatotopy in humans, and gives a brief overview of research on plasticity in the somatosensory system. Chapter 3 is a publication entitled *"Somatotopic organization of human somatosensory cortex: a comparison of EEG, MEG, and fMRI methods."* (Cheyne et al., 1998; *Brain Topography Today)*. This paper compares transient MEG and EEG somatotopic maps within the same subject, showing that each method appears to be imaging the same brain activity.

Chapter 4 reports an experiment which was undertaken to determine whether there are more efficient ways to map the somatosensory cortex than were used in the experiment of Chapter 3. Chapter 4 also evaluated the stability of somatotopic maps when subjects were tested for five repeated sessions under constant task conditions. Chapter 5 is a publication entitled *"Effect of multiple digit frequency discrimination on somatosensory representations in humans"* (Liu et al., 2000; Neuroreport). Here we provide evidence that somatotopic representations of the fingers can be dynamically fused or segregated, depending on the pattern of stimulation delivered to the digits during a somatosensory discrimination task. The results suggest that somatotopic representations are not statically fixed in the adult human brain but are altered by sensory experience to reflect the pattern of input experienced by the subjects on behavioral tasks. Finally, Chapter 6 serves as the conclusion.

Chapter 2

Organization and Dynamics of the Somatosensory Pathway

This review chapter outlines the somatosensory pathway from the skin organs responsible for transduction of tactile stimulation to the pathways ascended through the spinal cord and their final cortical projection targets. The chapter then details the literature describing EEG (electrical) and MEG (magnetic) somatosensory evoked fields and their use in mapping the somatosensory cortex. Finally, the chapter turns to the question of map dynamics and plasticity observed in the adult animal and human somatosensory system.

1. The Somatosensory Pathway

The mechanoreceptors that process tactile stimuli (perception of pressure, vibration, and texture) can be divided into two functional groups. *Slowly adapting* (SA) mechanoreceptors respond continuously to a persistent stimulus, while *rapidly adapting (RA)* mechanoreceptors respond at the onset and termination of a stimulus, but not throughout the duration of the stimulus (Dykes & Gabor, 1981). Another feature that helps classify mechanoreceptors is their proximity to the skin surface. Mechanoreceptors in the superficial digit epidermis are referred to as *type I* mechanoreceptors, whereas receptors deeper in the skin dermis are referred to as *type II.* Each type of mechanoreceptor also differs in part by the amount of stimulated skin surface that will activate a particular mechanoreceptor. The area of the periphery that, when stimulated, activates a mechanoreceptor is called the *receptive field* for the mechanoreceptor.

The superficial glabrous (hairless) skin of the fingertips contains two types of mechanoreceptors: the slowly adapting *Merkel's receptor* (SA-I) and the rapidly adapting *Meissner's corpuscle* (RA-I). The receptive fields of these mechanoreceptors are small (2-4 mm) which enables the resolution of fine spatial differences (Vallbo & Johannson,

1984). There are also two types of subcutaneous mechanoreceptors that serve both glabrous and hairy skin: the slowly adapting *Ruffini's corpuscle* (SA-II) and the rapidly adapting *Pacinian corpuscle* (RA-II). These receptive fields are much larger (>5mm) enabling the resolution of only course spatial differences (Vallbo & Johannson, 1984) (See Figure 1).

In the superficial skin, the SA-I Merkel's receptors are densely distributed at the distal glabrous phalange of the human hand and constitute approximately one-fourth of the 17,000 tactile units of the hand (Johansson and Vallbo, 1979). Microelectrode recordings indicate that the SA-I afferents respond throughout the period of skin indentation, including stimulation periods that persist for several seconds. Depending on the rate of indentation, a large transient indentation response can be observed (Johansson and Vallbo, 1979). Single electrical pulses are not felt; however, increases in stimulation frequency result in feelings of increased pressure at a skin location corresponding to the receptive field (Johansson and Vallbo, 1979). SA-I receptors are therefore thought to be important for

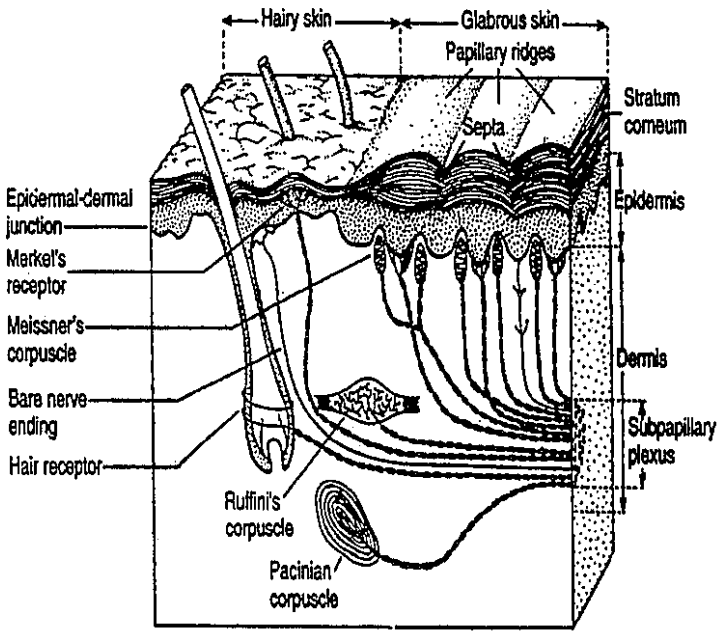

Fig. 1. Cross section of skin showing the location of the various hairy and non-hairy (glabrous) skin of primates. The superficial (*type I*) Meissner and Merkel's receptors and the subcutaneous (*type II*) Pacinian and Ruffini's corpuscles are shown. From Perl, 1968.

mediating the sensation of static pressure and providing edge and texture information (Johansson and Vallbo, 1979).

The most prominent receptor in the hand, the Meissner's corpuscle (RA-I), comprises approximately half of all tactile receptors in the hand, and are densely distributed in the glabrous skin of the distal phalange (Johansson and Vallbo, 1983). Microelectrode recordings indicate that RA-I receptors respond only to changes in skin indentation, and not to steady indentation (Srinivasan and LaMotte, 1987). Single electrical pulses of the RA-I receptors of the human hand result in a frequency following 'tap' sensation corresponding to the receptive field. Low frequency stimulation (1-5 Hz) produces a "frequency following" sensation, with higher frequencies merging into the sensation of "flutter" 5 – 40 Hz (Johansson and Vallbo, 1983).

The second class of slowly adapting receptors (SA-II) terminate in Ruffini's corpuscles, which are located deeper in the skin than the SA-I receptors (Darian-Smith, 1984). These receptors constitute approximately one-fifth of the hand's tactile afferents, and have large and poorly defined receptive fields (Johannson & Vallbo, 1979). The receptors are concentrated near the nail bed or skin folds on the digit or palm, and are sensitive to skin stretch. Electrical stimulation of a single SA-II receptor is not felt; however, there is psychophysical evidence that SA-II channels participate in the sense of touch and proprioception (Bolanowski et al., 1987).

The second class of rapidly adapting receptor is the Pacinian corpuscle (RA-II), which is located in subcutaneous fat and the tendon attachments of the ventral but not dorsal finger receptors (Darian-Smith, 1984). These receptors are relatively large (~1mm) and few in number (10-15%) (Johannson & Vallbo, 1979). The Pacinian

corpuscle can be activated by gently blowing on the skin, and it responds to the indentation and release of a probe, but not to steady indentation. Electrical stimulation of the Pacinian corpuscle in the human hand is not felt at low stimulus rates, but is perceived as a tickle or vibration at high stimulus rates, with the sensation restricted to a large diffuse receptive field (Johannson & Vallbo, 1979). Whereas the RA-I receptors respond with lowest thresholds in the 30-40 Hz range, Pacinian receptors have thresholds in the 250-350 Hz range, and thus appear to be particularly sensitive to high frequency vibration (Johannson & Vallbo, 1979).

Dorsal Root

Information about tactile events is transduced by the mechanoreceptors and conveyed by afferent fibers that enter the spinal cord through the dorsal horn. All sensory neurons have their cell bodies outside the spinal cord in a clump called a dorsal root ganglion. The sensory neurons are unique because unlike most neurons, the signal does not pass through the cell body. Instead, the cell body sits off to one side, without dendrites, and the signal passes directly from the distal axon process to the proximal process (Kass and Pons, 1988). The proximal end of the axon enters the dorsal half of the spinal cord, and bifurcates, with collateral relays terminating in the dorsal horns of the spinal gray matter while the axon projects upward along the dorsal white matter to the medulla-spinal cord junction (Dykes and Terzis, 1981). At the medulla, the primary afferents finally synapse (Kass, 1990). The neurons receiving the synapse are now called the secondary afferents. The secondary afferents cross immediately, and form a new tract on the opposite side of the brainstem (Kass, 1990). This tract of secondary afferents will

ascend all the way to the thalamus. Once there, they synapse, and a third and final neuron will extend up to synapse in the cerebral cortex (Kass and Pons, 1988).

The afferent pathway in the spinal cord has several divisions. The ascending spinal cord pathway or *dorsal column* is comprised of two separate tracts. The medial gracile fasciculus (gracile means 'slender'; fasiculus means 'a collection of neurons') carries all of the information from the lower half of the body (legs and trunk), while the cuneate fasciculus (cuneate means 'wedge shaped') carries information from the upper half (arms and trunk) (Kass, 1990). In the medulla, each tract synapses with a nucleus of the same name. The gracile fasciculus axons synapse in the gracile nucleus, and the cuneate axons synapse in the cuneate nucleus. The secondary afferents leave these nuclei and immediately cross, lining up in the ventral medulla. The new tract that they form is called the medial lemniscus (midline ribbon), and it ascends upwards through the brainstem. In the pons, the medial lemniscus begins to flatten out as the pontine nuclei enlarge beneath it. At the midbrain the medial lemniscus arcs laterally and dorsally in order to connect with the thalamus (Smith and Deacon, 1984).

Thalamus

The major thalamic nuclei receiving afferent input have been determined for squirrel monkeys and other primates with Nissl and other staining procedures (Dykes et al., 1981). The largest of these is the ventral posterior nucleus (VP). This nucleus is architectonically distinct and contains a complete, albeit compressed somatotopic representation via SA-I and RA-I afferents (Dykes et al., 1981). Input from the trunk and limbs terminate on cells in the lateral division of the nucleus (ventral posterior lateral nucleus), while input from the face projects to the medial division (ventral posterior

medial nucleus). Neurons in the ventroposterior (VP) lateral and medial areas project to different parts of primary somatosensory cortex (SI: areas 3a, 3b, 1, 2) with approximately 75% of VP neurons projecting to cortical area 3b. VP also receives dense feedback projections from both of these areas (Mayner and Kass, 1986). Both RA and SA afferents project from VP to 3b, however, it appears that RA and not SA afferents also project to area 1 (Kass, 1979). From primary somatosensory area 3b, neurons then project to Broadmann's areas 1 & 2 and to secondary somatosensory cortex (SII) (Kass, 1993).

The dorsal posterior portion of VP is thought to serve as a second distinct relay nucleus of somatosensory thalamus, labeled the ventroposterior superior nucleus (VPS) (Dykes, 1983). The VPS is considered distinct as it contains a separate representation of the body surface, has anatomically separate inputs and outputs and is histologically distinct from VP (Kass, 1993). Afferent receptors carrying joint and deep muscle spindle activations project to VPS and then to cortical areas 2 and 3a (Pons and Kass, 1985).

Cortex

While each of the four areas of primary somatosensory cortex (3a, 3b, 1 & 2) receive input from all areas of the body surface, Kass et al. (1979) have observed that one tactile modality tends to dominate each area in SI. In area 3a the dominant input is from the deep muscle stretch receptors; in area 3b it is input from SA-I and RA-I cutaneous receptors; in area 2 it is deep pressure receptors; and in area 1, Pacinian receptors (Kass et al., 1979). Figure 2 shows an illustration of the somatosensory pathway from the periphery to the six neocortical layers of the cortex. Thalamocortical projection terminals synapse principally in layer IV. Input from each digit projects to neurons within a

"cortical column". Each column is therefore tuned not only to a specific digit, but also to specific classes of receptors.

Cortical Columns

Mountcastle (1957) observed that neurons in all layers of the somatosensory cortex of the cat and monkey (Powell & Mountcastle, 1959) can be activated by stimulation of peripheral tissue, and that a single neuron responds to a specific somatosensory sub-modality (pressure, hair movement, etc.). These experiments also showed that individual neurons were activated only by stimuli applied to a particular area of skin. All neurons observed in vertical penetrations of the cortex responded to the same somatosensory sub-modality. The latter feature, which is illustrated in Figure 2, has given rise to the concept of the "cortical column" (Mountcastle, 1957) in which neurons sharing similar receptive field properties are clustered together in a columnar arrangement, with neurons in adjoining columns representing adjacent surfaces of the sensory epithelium.

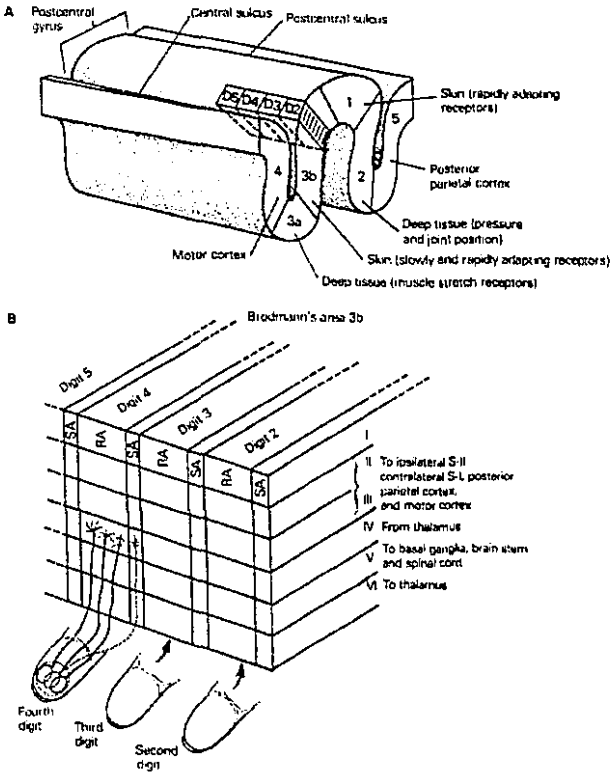

Fig 2 Columnar organization from the individual receptor modalities is shown. Panel A illustrates the Broadmann's areas 3a, 3b, 1 and 2 are primarily from one type of receptor. Panel B shows the expanded columns from Panel A. Area 3b cortical columns for digits 2-5 receive both RA and SA cutaneous receptor input from tactile stimuli. From Kass et al., 1979.

The activation of columns of neurons gives rise to extracellular field potentials which can be recorded subdurally, or from the scalp. These are called "Somatosensory Evoked Potentials" (SEPs), and I will be turning to them next.

2. Somatosensory Evoked Potentials and Magnetic Fields

Much of what has been learned about the somatosensory pathway has been made possible by invasive procedures describing the intracellular activity of single neurons. This procedure can only be done at the expense of the neuron and therefore at the expense of the subject as well. Noninvasive procedures have also been developed which record the collective activation of many hundreds of thousands of neurons. The electroencephalogram (EEG) is one popular technique for the clinical and experimental study of human brain function. EEG records the ensemble properties of the cerebral cortex as observed from the surface of the scalp.

Electroencephalography

EEG recorded from the scalp's surface reflects the activation of neurons in the underlying cortex. Extracellular currents flow though the interstitial space between neurons as *volume currents,* or ionic currents that propagate through the extracellular space in biological tissue. Potential changes recorded from the scalp are generated by the summed ionic currents of thousands of neurons located under the recording electrode. Figure 3 shows the path of excitatory inputs which synapse with pyramidal cells at cortical layers 2 and 4. Thalamic inputs synapse in deeper cortical layers (layer 4), while axons projecting from cortical sources synapse at higher cortical levels (layer 2). Figure 3 shows that scalp recorded negativity and positivity are due to current *sinks* (current flowing into the neuron) and *sources* (current flowing out of the neuron) produced at the

postsynaptic membrane by excitatory axons which synapse at the different cortical layers. Pyramidal cell activity contributes more to the EEG than nonpyramidal cell activity because pyramidal cells are oriented parallel to one another, and their dendrites are oriented perpendicular to the cortical surface. The synaptic potential generated on the dendrites is relatively free of spatial cancellation because the dendrites are oriented parallel to each other, perpendicular to the cortical surface (Martin, 1993). However, these potentials are susceptible to distortions (spatial blurring) produced by the passage of the volume conducted current through the tissue and fluids of the head (skull, skin or CSF).

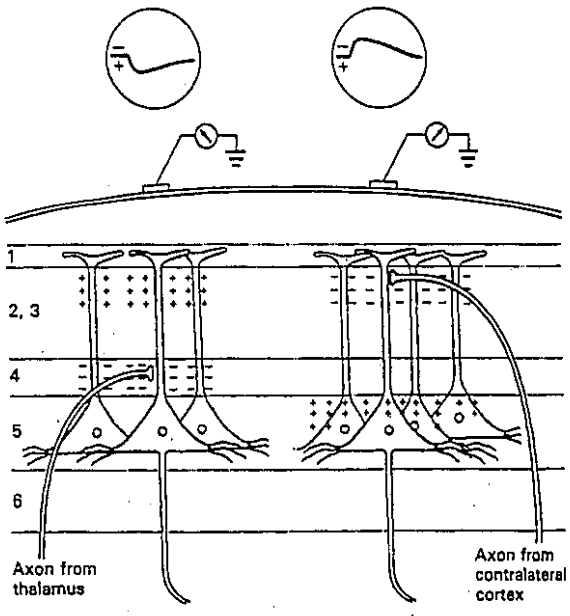

Fig. 3. Scalp recorded current flow is dependent on the depth of synaptic activity. Upward deflections represent negative potentials due to activity of near excitatory synapses. Deeper cortical excitatory synapses produce positive potentials at the scalp. From Martin, (1993).

Magnetoencephalography

One recently developed brain imaging technique that avoids the problem of volume conduction is magnetoencephalography (MEG). Developed in the late 1960's (Cohen, 1968), MEG detects *intracellular* electrical currents which flow in a spatially coherent direction owing to the parallel arrangement of the dendrites. These intracellular currents generate a small magnetic field around them, in accordance with the right hand rule of physics, which can be detected by magnetic sensors (SQUIDS, or superconducting quantum interference devices; about 150 sensors are used in modern whole-head MEG systems) placed near

the surface of the scalp. The magnetic fields generated by intracellular currents are not impeded by the tissues of the head and pass through them (skull, cerebrospinal fluid, skin, etc.) without distortion (Williamson and Kaufman, 1981). These properties appear to give MEG a significant advantage when attempting to localize the generators of event-related cortical activity (Cheyne et al., 1991). One potential disadvantage of MEG is that the magnetic fields that travel outside the head typically arise from cortical columns oriented tangential to the cortical mantle. Magnetic fields generated by radially oriented currents in the brain are unlikely to travel outside of the head, and therefore cannot be detected by the MEG sensors (Williamson and Kaufman, 1981).

The great majority of non-invasive research on the human somatosensory pathway stems from EEG research; however, MEG is being adopted in hospitals and research facilities as a powerful functional brain imaging tool. The next section reviews the literature on somatosensory evoked potentials measured by EEG and MEG.

Somatosensory Evoked Potentials

Somatosensory evoked potentials have enjoyed a long history as an experimental and clinical tool for the identification of specific brain generators involved in processing somaesthetic stimuli from the periphery. These potentials can be generated by either electrical stimulation which activates all receptor pathways (RA I, II; SA I, II) in the underlying nerve or skin, or by mechanical stimulation which can segregate receptor pathways on the basis of their frequency selectivity. Another distinction that will be important to this thesis is whether stimulation is delivered at long interstimulus intervals such that the brain response to one stimulus subsides before the next stimulus occurs ("*transient*" SEPs, stimulus frequency typically below 3 Hz), or whether the interstimulus

interval is shortened such that successive brain responses overlap (*"steady state"* SEPs, stimulus frequency typically above 3 Hz). In the following sections I summarize current findings regarding SEPs, distinguishing transient from steady-state SEPs, and within the transient case, SEPs evoked by electrical and mechanical stimuli.

Transient SEPs Evoked by Electrical Stimulation

Because electrical stimuli are easily delivered, the majority of information on SEPs as been gained from electrical stimulation studies. Three broad classes may be distinguished on the basis of response latency, (1) short latency SEPs (<18 ms), (2) middle latency SEPS (latency between 20-70 ms), and (3) long latency SEPs (>80 ms). In addition to latency, SEPs are also labeled by their polarity at the scalp electrode, N designating a negative-going potential and P a positive-going one.

Short latency SEPs elicited by electrical stimulation of the median nerve or a digit nerve can be observed from an electrode at the base of the neck (i.e., the supraclavicular fossa or Erb's point), or from scalp electrodes. The 'N9' potential is observed as a negative peak at Erb's point 9 milliseconds (ms) after stimulus onset, and reflects activation in the brachial plexus (Kimura et al., 1978). Activity from the cervical cord and medulla can be recorded from the head and neck 11 to 15 ms after stimulation at the wrist or digits. The scalp positivity at 13 ms (P13) is thought to be generated post-synaptically in the dorsal column nuclei and the observed positivity at 14 ms (P14) is thought to be generated from synapses in the medial lemniscus and its branches to various mesencephalic nuclei in the medulla and lower pons (Chiappa, 1990). Desmedt and Cheron (1981b) first described the N18 as a long lasting negative shift that immediately follows P14. The N18 is thought to be generated in the thalamus (with late

negativity possibly arising from thalamocortical projections or primary cortex) and the subsequent positivity generated from parietal sensory cortex (Chiappa, 1989). Thus short latency SEPs are believed to reflect propagation of nerve impulses in nuclei of the somatosensory projection pathway prior to the cortex. Short-latency SEPs can provide information of value for medical assessment, but the responses are relatively small and require extensive signal averaging for their visualization. They are not considered further in this thesis.

Middle latency SEPs (20-70 ms) are generally believed to signal the arrival of somatosensory information at the cortex (see Figure 4). The first prominent component is a P20/N30 complex which is recorded at electrodes anterior to the central sulcus (latencies of 20 and 30 ms, respectively, Panel A, upper left trace, Figure 4). A polarity-reversed mirror image is recorded at electrodes posterior to the central fissure (N20/P30, Panel A, upper right trace), suggesting a neural generator in area 3b of somatosensory cortex for these components. An intervening component with a latency near 25 ms is

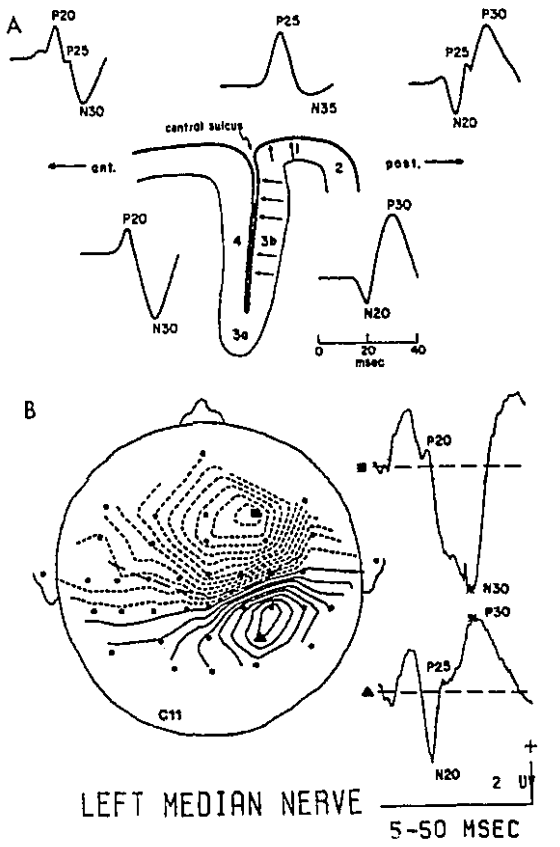

Fig. 4. Median nerve stimulation produces several potentials observed between 18 and 30 ms. The generator of the N20 response is illustrated as a tangential dipole in area 3b (Panel A). Panel B shows the topographic map of the current reversal (simultaneous posterior negativity and anterior positivity) at 20 ms. From Allison et al., 1986.

also observed at electrodes positioned above the central sulcus, called the P25 (Panel A, upper middle, Figure 4). Allison et al. (1980) attributed these observed topographies to two polarity-reversing dipolar sources located in primary somatosensory cortex (SI), one tangentially oriented in area 3b and one radially oriented on the anterior crown of the post central gyrus (Panel A, Figure 4, anatomical drawing). The large fold between motor and somatosensory areas results in a large amount of area 3b buried in the central sulcus relative to the cortical surface. Panel B of Figure 4 shows the scalp distribution of the electrical field at 20 ms and the SEP recorded from anterior and posterior electrodes from 5 to 55 ms. Dipolar traces seen at 20 ms and 30 ms in the SEP are attributed to a reversing cortical source in area 3b, and the inflection at 25 ms to the source in area 1 on the posterior crown of the cortex.

A second middle latency SEP complex appears after the P20/N30, the P40/N60 which is also observed contralateral to the stimulated hand. This component has not been studied as extensively as its preceding P20/N30. Evidence from patients with well-localized thalamic infarcts suggests that this potential reflects activity from projections of non-specific thalamic nuclei to the cortex (Yamada et al., 1981). The P40 is thought to originate from parietal regions and the N60 in the pre-Rolandic area (Mauguiere et al., 1983; Colon et al., 1985). Unlike the prior unilateral distribution of sources of the previous SEP components to the contralateral hemisphere, the sources of the N60 are believed to be highly distributed in both hemispheres.

Several long latency SEPs (>80 ms) have also been identified but are of little clinical relevance. The P100/N140, P200/N260 and P300/N360 complexes are generally maximal at vertex and of large amplitude and progressively slower in frequency (Colon

and Comi, 1990). Based on the results of depth electrode studies, the generators of the large N140/P200 complex are assumed to be the corpus callosum (Goff et al., 1978) or somatosensory associative cortex (Desmedt, 1981). Little is known about the location of generators that follow these potentials. This is probably due to the diffuse patterns of activity, individual differences, and the effect of cognitive influences such as attention.

Transient SEPs Evoked by Mechanical Stimulation

There are advantages and disadvantages to using an electrical stimulus to study the somatosensory pathway. Stimulating the peripheral nerves electrically is a technically simple procedure requiring a couple of 'ring' or 'cup' electrodes and an inexpensive (commercially available) electrical stimulator. The intensity and latency of stimulation are easily controlled and produce highly synchronous responses with a large signal to noise ratio. Another benefit of stimulating subjects electrically is that it is silent stimulation, and will not produce stimulus-locked auditory evoked potentials. Disadvantages to electrical stimulation include a lack of specificity regarding the types of fibres activated and the failure (in median nerve preparations) to activate nerve endings. This may present difficulties when attempting to detect functional changes. Finally, the subjective sensation evoked by electrical stimulation has been described unfavourably as unnatural and non-specific with a limited range of stimulus intensities. (Pratt and Starr, 1986).

Despite these differences in stimulation technique, there are qualitative similarities in the SEPs evoked mechanically and electrically. An early latency complex is seen following mechanical stimulation at approximately 30 to 35 ms (Hamalainen et al., 1990; Forss et al., 1994). Its generators appear to reside in area 3b in accordance with

the Allison model. Latency of these responses is not always in precise agreement owing to differences in stimulus procedure, but are typically within a 10 ms range. However, three differences between electrically and mechanically induced responses should be noted. First, short latency SEPs are not often observed with mechanical stimulation, perhaps because these responses which are of low amplitude when evoked electrically are not sufficiently synchronized when evoked mechanically. Second, the P20/N30 complex tends to be more prominent when induced electrically, probably because of increased synchronization. Third, a later component peaking near 50-60 ms (the "P50" component) is very prominent following mechanical stimulation. This component is less prominent in electrical recordings, perhaps because electrical stimuli activate additional afferent pathways. The experiments of this thesis and somatotopic mapping studies to be reviewed below will show that the cortical sources of the P50 component appear to be situated in area 3b. Animal studies indicate that afferents arising from Meissner corpusles which are activated by mechanical stimuli project to cortical columns in area 3b of somatosensory cortex (Kaas et al., 1979).

Gardner et al., (1984) used controlled mechanical stimulation (airpuff) of the skin to compare the timing of single unit responses in primary somatosensory cortex (SI) of alert monkeys to SEPs elicited at the cortex in the same monkeys. This was done in order to correlate cortical neuronal excitation and inhibition with the surface recorded positive and negative components. Single unit responses were recorded to mechanical airpuff stimuli presented to the wrist (0.5 – 4 sec variable inter-stimulus interval). Neurons in area 3b and 1 of SI cortex response included a repetitive train of impulses lasting 15-30 ms, followed by a period of inhibition 60-100 ms in duration (Gardner et al., 1984). The

maximum firing of neurons in area 3b coincided with the P15 wave, which was followed by a smaller P25. The early positive complex was terminated by a large, relatively long lasting negative potential with a poorly defined peak (N43) which was observed to begin approximately 30 ms after airpuff onset, and last until approximately 60 ms (Gardner et al., 1984). Of interest to the present thesis, this potential is temporally consistent with the P50 response. Also of interest, the researchers noted that there was no observed SEP that corresponded to the human median nerve N20 potential. The authors also observed that both single unit responses and SEP amplitudes were largest when three closely adjacent skin sites were stimulated simultaneously than when any one of them was stimulated alone (Gardner et al., 1984). This question of the summation of somatosensory responses evoked simultaneously in adjacent digits is considered further in Chapter 5 of this thesis.

Hamalainen et al. (1990) were first to name the "P50"mechanical response. Using an electromechanical vibrator, these researchers measured SEPs to single transient pulses of *slow* (24 Hz) or *fast* (240 Hz) tactile stimulation, or to trains of *slow* (24 Hz) or *fast* (240 Hz) stimuli of 300 ms duration. All stimuli were delivered to the middle finger at a frequency of 1.5 Hz. The researchers observed a reliable contralateral P50 response, followed by a contralateral N70, bilateral P100 and contralateral N140 to both slow and fast transient pulses, with the greatest difference between the two stimuli observed as a larger amplitude N140 following the *fast* (240 Hz) pulse. Responses to vibratory trains included a relatively small contralateral P50 and N70 response to slow and fast frequency stimulation and larger bilateral P100 and N140 responses. The authors concluded that the contralateral P50 responses to transient stimuli are generated from contralateral SI cortex

while the large bilateral P100 response brought on by high frequency vibration stimuli may be the result of neural activity arising from secondary somatosensory cortex SII.

A recent MEG experiment by Forss et al. (1994) compared somatosensory responses to airpuff stimulation to the dorsum of the proximal phalanx to that of 3 Hz electrical stimulation of the median nerve. The researchers described the initial responses to airpuff stimulation occurring at 32 ms, with the largest responses at 48 and 65 ms. Forss et al., (1994) described all of theses sources as dipolar, with equivalent current dipole solutions localized in SI cortex. The responses to electrical median nerve stimulation peaked at 21 ms (N20), at 36 ms (P35m) and 58 ms (P60m) which were also modeled as dipole sources from SI. The authors noted that the latency of the responses to airpuff stimulation was significantly longer than that of electrical stimulation, even after factoring out the 2.5 ms delay caused by stimulating a more distal site (Forss et al., 1994). The mean dipole moment was observed to be significantly weaker for airpuff than electrical stimuli which was taken as evidence by the authors that the airpuffs stimulate a smaller subset of afferent fibers than the electric stimuli. The authors concluded that the observed differences in SI sources reflect differences in the stimulation. Forss et al. (1994) concluded that primary somatosensory cortex encodes the physical details of tactile stimulation, such as the size of the stimulated skin area, and the types of receptors activated.

Steady-state SEPs

Responses evoked by stimuli which follow each other at sufficiently long stimulus intervals such that the brain response returns to the initial state before the next stimulus begins are referred to as *transient responses* (Regan, 1982). Conversely, if the

inter-stimulus interval is shortened such that the transient responses overlap, the response is referred to as a *steady-state response* (Regan, 1982). In a linear system, the transient response has a fixed linear relationship to the steady-state response, and the two responses can be thought of as providing alternative pictures of the same phenomenon. While there is evidence that auditory and visual pathways show some non-linear properties, and this issue is currently debated (e.g. Gutschalk et al., 1999; Pantev et al, 1996; Regan, 1989), there is little information comparing transient and steady-state responses in the somatosensory system. There are however, practical advantages of steady-state over transient procedures. The data are gathered more quickly with steady state, which reduces recording time. Also, analysis in frequency domain may increase the signal to noise ratio. These advantages may be important for studies of plasticity in the somatosensory system, one of the objectives of this thesis. The measurement procedure should be as efficient as possible, in order to reduce the possibility that the measurement procedure itself may reverse cortical remodeling induced by training. Steady state procedures which gather data quickly and afford analysis in the frequency domain may reduce this risk.

Namerow et al. (1974) were the first to investigate the effect of high frequency steady-state stimulation on the recorded electrical brain response (EEG). Electrical median nerve stimuli were presented at 12 Hz, 20 Hz, 40 Hz, 60 Hz, 80 Hz, 100 Hz, 160 Hz and 200 Hz in trains of 250 ms duration spaced 2 seconds apart. Namerow et al., (1974) used narrow-band filtering to isolate and quantify the response at the stimulation frequency. Namerow et al., (1974) observed the largest responses over contralateral post-Rolandic scalp and a monotonic drop in peak-to-peak amplitude with increasing

frequency. Most interestingly, Namerow et al., (1974) described a topographic phase reversal over contralateral somatosensory areas for stimuli as high as 60 Hz and 100 Hz.

More recently Garcia-Larrea et al. (1992) observed topographical maps for median nerve stimulation delivered at 2 Hz, 5 Hz, and 10 Hz. They observed that N20 amplitude was significantly decreased by increasing the stimulation rate from 2 Hz to 10 Hz. Due to the observation that increases in frequency above 5 Hz significantly distorts the early SEP components, Garcia-Larrea et al. (1992) concluded that there was no optimal higher rate for SEP recording. Another recent observation on the effect of increasing stimulation frequency was performed by Manzano et al., (1995). Somatosensory evoked responses were observed to 3 and 30 Hz electrical stimulation of the median nerve. Manzano et al., (1995) also observed that higher rates of stimulation reduced the amplitude of the early N9, N/P 13 and N20 components.

Noss et al. (1996) was first to use amplitude modulated electrical pulses to generate SEPs. Noss et al. (1996) designed an experiment to examine directly the feasibility of reducing the data recording time by using steady-state stimulation. The researchers compared transient 4 Hz median nerve stimulation to steady-state stimulation at 7.4 Hz, 14.7 Hz, 25.6 Hz and 41.2 Hz (presented as sinusoids with 100% modulation depth on a 150 Hz carrier). Noss et al. (1996) reported that, in contrast to the transient stimulation, the steady-state responses showed a prominent signal to noise ratio (SNR) after as little as 10 seconds of stimulation.

Snyder (1992) observed steady-state mechanical vibration SEPs to whole hand stimulation over a number of different stimulus frequencies (2 Hz, 3 Hz, 5 Hz, 7 Hz, 11 Hz, 17 Hz, 26 Hz, and 40 Hz). Two pertinent results from this study were that the evoked

response (RMS amplitude) decreased with increasing modulation frequency, and that the frequency producing the highest signal to noise ratio (from 2 Hz to 40 Hz) was 26 Hz. Snyder et al. speculated that the peak at 26 Hz may have been caused by a resonance-like phenomenon. Dipole analysis of the SEP localized its sources to the contralateral cortex, however, due to the large stimulation surface, digit somatotopy could not be observed. Recently, Tobimatsu et al. (1999) replicated the Snyder et al. (1992) experiment using EEG and a slightly different range of amplitude modulated vibration stimuli. Tobimatsu et al. (1999) presented a constant carrier of 128 Hz and varied the modulation frequency from 5-30 Hz (5 Hz, 7 Hz, 11 Hz, 14 Hz, 15 Hz, 17 Hz, 21 Hz, 25 Hz, and 30 Hz) to the palmar surface of the hand. In contrast to Snyder et al.'s (1992) results, the researchers found the greatest SNR at stimulation frequency of 21Hz. In agreement with Snyder, Tobimatsu et al. (1999) considered the peak in responsiveness of the somatosensory system occurring between 21-26 Hz to reflect some resonance-like phenomenon that occurs to frequencies in the flutter vibration range.

3. Somatotopic Maps

Somatosensory evoked potentials can be used to measure somatotopy. The approach is to fit equivalent current dipoles to the electrical or magnetic field patterns evoked by stimulation of each finger, and then co-register the dipoles on neuroanatomy measured by MRI for each subject. The magnetic (MEG) or electrical (EEG) response can be elicited by electrical and mechanical stimulation of the fingers, and different components of the SEP can be used for dipole fitting. These components may or may not localize to the same area of the brain, but because their latencies are different, they do reflect different functional activations.

Buchner et al. (1995) recorded 64 channel EEG during electrical stimulation of the digits 1, 3 and 5 of the hand and the median nerve. Square wave pulse stimuli (0.2 ms duration) were delivered at a repetition rate of 3.1 Hz. Four replications of 1500 sweeps were averaged for each finger and median nerve. To summarize briefly, using dipole source analysis these investigators first placed a dipole in the area of the brain stem and adjusted its location, orientation and strength to describe the P14 component of the SEP. With this dipolar source held constant, a second dipole was placed in the somatosensory cortex contralateral to the site of stimulation and adjusted to describe the tangential P20/N20 component of the SEP using a 95% minimal residual variance solution. In 6 out of 8 subjects, the second dipole was observed to be somatotopically organized along the central sulcus with 5th digit medial and superior to the first. Two subjects showed interleaving of digits (mediolateral order 3, 1, 5; and 1, 5, 3). Repeated measurements were not taken in this experiment, however, mean replication error for dipole sources calculated on split-half averages were reported to be between 3.2 mm and 5.8 mm.

Using a 14 channel magnetometer, Suk et al., (1991) used dipole analysis to determine the cortical sources of responses evoked by transient bursts of 250 Hz stimulation delivered by piezoelectric buzzers at 2Hz (variable 400 - 600 ms ISI - 100 ms duration) to the 1st 2nd and 5th digits. Peak reversal occurred between 60 and 63 ms with dipole localization of the P50 field restricted to a small area of contralateral post central gyrus. In all cases (N=3) cortical sources representing the 5th digit were localized superior to sources representing digits 1 and 2, in accordance with Penfield's somatotopy (Suk et al., 1991).

Similar results have been obtained using a pneumatic stimulus. Yang et al. (1993) stimulated 66 tactile sites (including the digits) while recording 37 channel MEG (1cm stimulus diameter; 450-550 ms variable interstimulus interval). Yang observed peak somatosensory responses between 40-89 ms which were localized with a single dipole model. The authors observed that the digits of the hand (both glabrous and dorsal surfaces) could be described using a single dipole model. Of note as well, both Yang et al. (1993) and Suk et al. (1991) observed similar somatotopic organization when dipole analysis was applied to the P50 response although the stimulation methods were quite different in these studies. It appears that the 100 ms bursts of 250 Hz vibration stimuli used in Suk et al., (1991) may produce responses similar to the transient response observed in Yang et al., (1993) using a transient 2 Hz pneumatic stimulus. The observations of Yang et al. (1993) were later confirmed by Nakamura et al. (1998) who demonstrated detailed somatotopic mapping using the same stimulus and 37 channel MEG. Nakamura et al. also calculated from dipole moment an estimate of the size of the cortical area believed to have been activated by stimulation. Dipole positions for body areas from the face, hands and toes were displayed as ellipses varying in size with dipole moment, and which Nakamura et al. (1998) described as generally consistent with Penfield's homunculus.

Somatotopy measured by the P50 component evoked by mechanical stimulation has recently been report by Braun & Schweizer et al. (2000) and by Braun & Wilms et al. (2000). In both of these experiments (the first measuring 128 channel EEG and the second whole-head MEG) dipole positions determined for the 1^{st} and 5^{th} digits were represented in polar coordinates, with the parameter polar angle representing dipole

position in the medial-lateral plane within the postcentral gyrus (area 3b). In both experiments dipole positions for the 5th digit were found to be more medial and superior than dipole positions for the 1st digit, in agreement with somatotopy measured in other functional brain mapping studies. These studies are noteworthy because the distance in polar angle between dipoles representing the digits also changed with task conditions. Braun & Wilms et al. (2000) found that the distance between cortical sources for digits 1 and 3 was diminished when subjects received regular sequential stimulation of the finger tips, compared to a condition in which subjects received random sequential stimulation of the finger tips. Braun & Schweizer et al. (2000) found that the distance between cortical representations for digits 1 and 5 depended on whether subjects received temporally synchronized stimulation of these digits or whether a discrimination was required among distinctive stimuli presented the fingers. These findings suggest that somatotopic maps are not statically fixed but can be modulated by task conditions.

EEG and MEG techniques reviewed above have shown considerable potential for mapping the organization of human somatosensory system noninvasively. In each experiment transient stimulation was employed (typically 1 - 2 Hz, maximum of 4 Hz) to evoke SEPS for dipole analysis. Although somatotopy was detected, a practical limitation is that the time required to collect data sufficient for analysis of individual subjects was long, typically 1-3 hours per subject. Measurement times of this duration are an impediment to investigating the short-term temporal dynamics of somatotopic maps. For example, do maps change quickly with attention and context, or must the stimuli be experienced for some period of time before changes are seen? Are maps modified by training on somatosensory skill tasks, and if so, how quickly do these

changes take place? In the following (concluding) section, I review evidence from animal studies which indicates that somatotopic maps in the adult brain are not statically fixed but appear to be remodeled by plastic mechanisms to represent the pattern of stimulation experienced on a task. Investigation of these dynamics in humans is desirable but could profit from more efficient methods of measuring somatotopy.

4. Plasticity

Traditionally, mammalian cortical organization was thought to be dynamic throughout early development up to some critical period of development, and immutable thereafter. Over the past decade, this view has been challenged by a wealth of experiments which demonstrate the ability of adult somatosensory cortex to reorganize following procedures that alter the pattern of sensory input delivered to it. Experiments have employed deafferentation, manipulations of temporal coincidence, and behavioural training in order to observe changes in cortical organization.

Deafferentation

Somatotopic reorganization has been most extensively demonstrated in primary somatosensory cortex (SI) following deafferentation. In a series of landmark experimental studies, Merzenich et al. (1983a; 1983b) documented, for the first time, the capacity of adult monkey cortical area 3b to reorganize following the removal of an input to somatosensory cortex. Merzenich et al. (1983a) performed a median nerve transection on a group of adult owl and squirrel monkeys which deactivates inputs from the glabrous (hairless) hand from D1 to the middle of D3. Merzenich et al. (1983a) observed that, before any nerve regeneration occurs, the deprived cortex becomes responsive to the adjacent cortical inputs from the dorsal surface of the hand. Merzenich et al. (1983a)

observed that a new somatotopic organization is created in which the cortical representation of the dorsal surfaces of digits 1-3 becomes many times larger than in normal animals, and the receptive fields for neurons in this altered cortex appear much smaller for cortical neurons representing the dorsal hand. The time course for such changes was observed to occur within hours of the nerve section (Merzenich et al., 1983b). Further work by Merzenich et al., (1984) investigated the effect of the complete removal of a single digit in owl monkeys. Microelectrode maps before and after removal of digit 3 revealed that the cortical territory normally activated by stimulating digit 3 became responsive to light touch on the glabrous surface of digits 2 or 4. These results indicate that reorganization following digit denervation depends in part on which inputs are removed. Transection of the median nerve subserving glabrous digits 1-3 results in a shift in tuning towards dorsal digit 1-3 inputs. Removal of both dorsal and glabrous inputs from digit 3 produces a shift in cortical tuning to the glabrous digits 2 and 4 (Merzenich et al., 1984).

The immediate shifts in somatotopic organization reported in these studies were attributed to the unmasking of previously silent lateral connections between neurons in cortical area 3b by deafferentation. More specifically, immediate changes may be the result of a reduction of activity-driven activation of inhibitory neurons and to a disruption of the normal balance between inhibitory and excitatory influences on neurons in the sensory map (Florence & Kass, 1995). It should also be noted that such deafferentation procedures do not always result in the complete re-activation of deafferented cortex. Garraghty et al. (1994) observed that much of the deprived cortex remains unresponsive to tactile stimulation following combined transection of the radial nerve with either the

median or ulnar nerves. Recently, Florence and Kass (1995) have proposed that small changes in the primary sensory inputs to the cuneate nucleus of the brainstem are responsible for the immediate shift in organization observed with deafferentation. Here, the authors argue that after denervation of the glabrous surface, the inputs from the hairy skin come to activate neurons in the cuneate nucleus that once responded preferentially to glabrous inputs (Florence & Kass, 1995). In cases where both hairy and glabrous skin are denervated, patches of quiescent cortex appear as neither input reaches the cuneate nucleus.

Merzenich et al., (1984) concluded that cortical somatosensory maps are dynamically maintained and are alterable as a function of use or nerve injury. These observations inspired a flurry of digit denervation experiments on other adult mammals including the raccoon (Turnbull & Rassmuson (1990, 1991), in the flying fox (Calford & Tweedale (1991a, 1991b, 1991c), and forelimb nerve transection in the cat (Dykes et al., 1995). The results of these studies supported Merzenich et al.'s (1993) observations that adult primate somatosensory cortex is capable of considerable reorganization including the development of new receptive fields and somatotopic organization within seconds or minutes following deafferentation procedures (Calford & Tweedale, 1998; Turnbull & Rassmuson, 1990). The changes reflect cortical dynamics and not necessarily the strengthening or weakening of synaptic connections by altered sensory experience (plasticity). Changes that take place over a longer time course (weeks to months) are thought to be the result of new patterns of input to the cortex that may allow for the expression of Hebbian-type changes to occur.

Temporal Coincidence

Clark. et al. (1988) examined the effect of increasing the temporal correlation of digit inputs of primates by the joining digits 3 and 4 surgically for several months. The surgical syndactyly procedure was used to test the hypothesis that single digit receptive fields are observed in normal monkeys because temporal decorrelation of tactile sensations arising from them favors segregation of their cortical representations. Following the surgical procedure, normal adult owl monkeys were allowed to live under normal experimental conditions for several (3-5) months of digital fusion. The normal adult owl monkey receptive fields in area 3b of the hand show discrete topographic organization, with receptive fields restricted to single fingers. After several months of digital fusion, however, the zones of discontinuity between digit 3 and 4 were replaced with a patch of cortex that responded equally to stimulation of digit 3 or 4 (see Figure 5). The borders of the adjacent digits 2 and 5 were observed to be normal and abrupt; however, newly formed multiple digit receptive fields were observed on the skin surfaces of both fingers 3 and 4 along the line of fusion. To investigate whether these changes were due to changes in peripheral or central nervous system, the

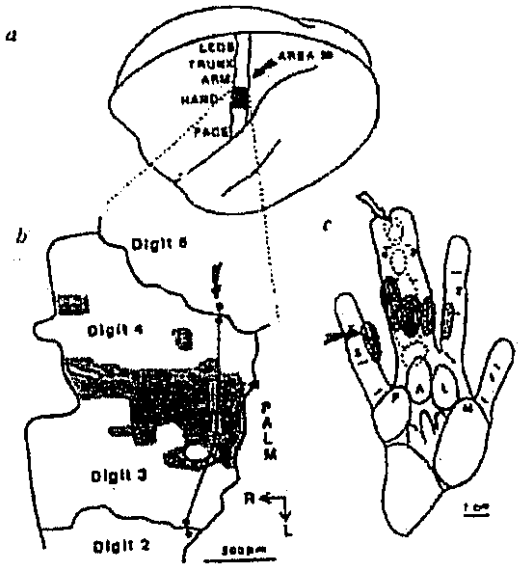

Fig.5. Cortical representation following cutaneous fusion of digits 3 and 4. Panel b shows a reconstruction of the cortex representing digit 3 and 4 after 5 months of digital fusion. The shaded area marks the cortical area demonstrating double digit receptive fields. Filled dots and squares in b mark recording cites in rostral-caudal (white arrow) and medial-lateral (black arrow) respectively. Receptive fields for these sites are shown on the hand drawing in panel c as open and shaded regions. From Clark et al. 1988.

receptive fields were mapped again immediately following surgical digit separation. The researchers observed that double digit receptive fields persisted following separation of digits 3 and 4. Clark et al., (1988) concluded that it is the temporal correlation of inputs that create and maintain receptive fields in somatosensory cortex, rather than any sharply-demarcated limitation of anatomical connections. This experiment and similar findings reported by Mogilner et. al. (1993) in human syndactyly patients whose digits were separated by surgery indicate a the effect of dramatically changing the pattern of afferent input. The question of whether similar results could be observed with less dramatic manipulations of temporal coincidence soon followed.

Learning Paradigms

Jenkins et al., (1990) were first to investigate whether reorganization would follow behavioural learning paradigms. Monkeys were trained to maintain contact with a rotating disk with 10 wedged-shaped groves on its surface in order to receive a food reward. The disk was rotated once per second producing a 20 Hz stimulus intended to activate a restricted patch of skin afferents in a nearly simultaneous fashion. The monkeys were required to maintain contact with this disk for 10 – 15 seconds in order to receive a banana pellet. Exposure to the training lasted from between 52 days to 278 days, and consisted of about 1.5 hours (~600 pellets) per day. Jenkins et al., (1990) observed that the area of cortex tuned to digits used for obtaining these rewards increased (see Figure 6), suggesting that more neurons acquired receptive fields on the digits as a consequence of tactile discrimination learning. The authors also observed that, in parallel with the appearance of new receptive fields, the size of each receptive field decreased to a fraction of normal. The authors concluded that, in support of Clark et al. (1988),

temporally coincident or nearly-coincident inputs play a major role in shaping cortical receptive fields and representational topographies. The role of attention and the question of whether such reorganization was correlated with improvements in behaviour on task relevant discrimination tests was beyond the scope of this experiment. However, these questions became the focus for a new series of experiments by Recanzone and his colleagues published in 1992.

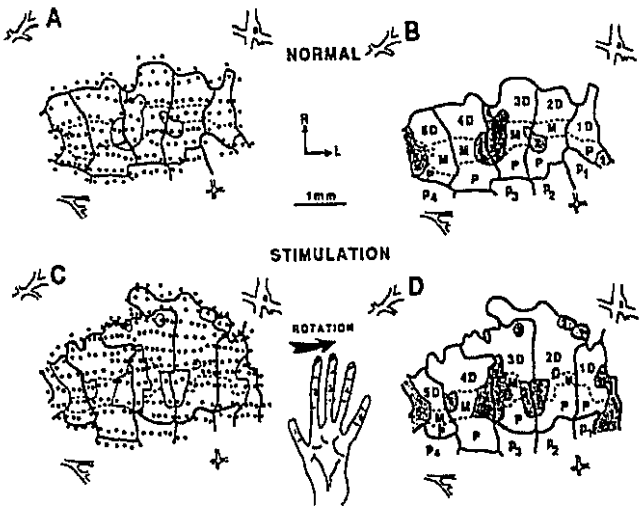

Fig. 6. Panel A shows the microelectrode penetration grid within area 3b for a normal owl monkey. Panel B shows the reconstruction of the hand area for one monkey before training. Panel C shows the penetration grid following 109 days involving stimulation on the rotating disk (~1.5 hrs per day). Panel D shows the post training reconstruction of the hand area. Skin surfaces stimulated on the behavioural task are indicated on the hand inset. Cortical representation for these skin surfaces expanded greatly (compare digit 2, 3 & 4 distal segments in panel B and D). From Jenkins et al., 1990.

Recanzone et al. (1992a; 1992b) trained adult owl monkeys to detect a difference in the frequency of a tactile stimulus sequentially applied to the glabrous surface of a single digit. Monkeys were trained over a 3-20 week long training period to detect small increases in frequency from a 20 Hz standard (S1) and upon detection, to break contact with the stimulus. The authors recorded psychophysical measurements over this training period, prior to microelectrode mapping of their somatosensory cortex. The authors observed that behavioral thresholds for detecting changes in the 20 Hz standard improved from a 6-8 Hz difference to a 2-3 Hz difference, and that these improvements in detection were correlated with topographic changes in the somatosensory hand area. Specifically,

the authors observed that the cortical representation of the restricted skin location involved in training was significantly greater in area (1.5 to 3 times) than homologous areas of skin on control digits. The receptive fields of neurons tuned to these skin areas were observed to be significantly larger than that of control digits; furthermore, the receptive fields of neurons responding to the trained finger came to be centered on the behaviourally trained skin site. Control experiments showed that these changes occurred only when animals were trained on the somatosensory discrimination task. Monkeys that received the same tactile stimuli but were trained to discriminate among concurrently present auditory signals did not show reorganization of the somatosensory cortex (Recanzone et al., 1992b).

Wang et al. (1995) extended the work of Jenkins et al.(1990) and Recanzone et al. (1992) by observing changes to somatosensory cortex as a consequence of behavioural training involving coincident stimulation of multiple digits. Wang et al. (1995) trained unrestrained owl monkeys to place one hand on a form-fitted hand grip and to discriminate tactile stimulus sequences delivered to the glabrous skin of the hand by two narrow bars. When raised, one bar made simultaneous contact with the distal phalanges of digits 2, 3 and 4, while the other bar, when raised, made simultaneous contact with the proximal phalanges of the same digits (see Figure 7c). Monkeys experienced indentations of 50 ms presented by each bar with a 200-300 ms inter stimulus interval; their task was to detect two consecutive indentations presented to the same phalange (Figure 7b). Monkeys were trained over a 4-6 week period including 300-500 trials per day. Following training, microelectrode measurement of somatosensory maps taken under anesthesia showed two large continuous zones of cortex, one representing proximal

finger surfaces and the other distal finger surfaces, in which neurons exhibited multiple digit receptive fields ("fusion"). In untrained monkeys neurons with multiple digit receptive fields are rarely observed, which suggested that such fields were induced by temporally coincident stimulation experienced on the discrimination task. In addition, a prominent band emerged between the proximal and distal phalanges in which all units responded exclusively to dorsal skin inputs (see Figure 7d). This finding was taken to suggest that cortical reorganization occurred as well for neurons that represented skin surfaces which were not struck simultaneously ("segregation"). Both effects (fusion and segregation) appeared to be the result of reorganization occurring in the cortex and not in thalamic nuclei projecting to the cortex.

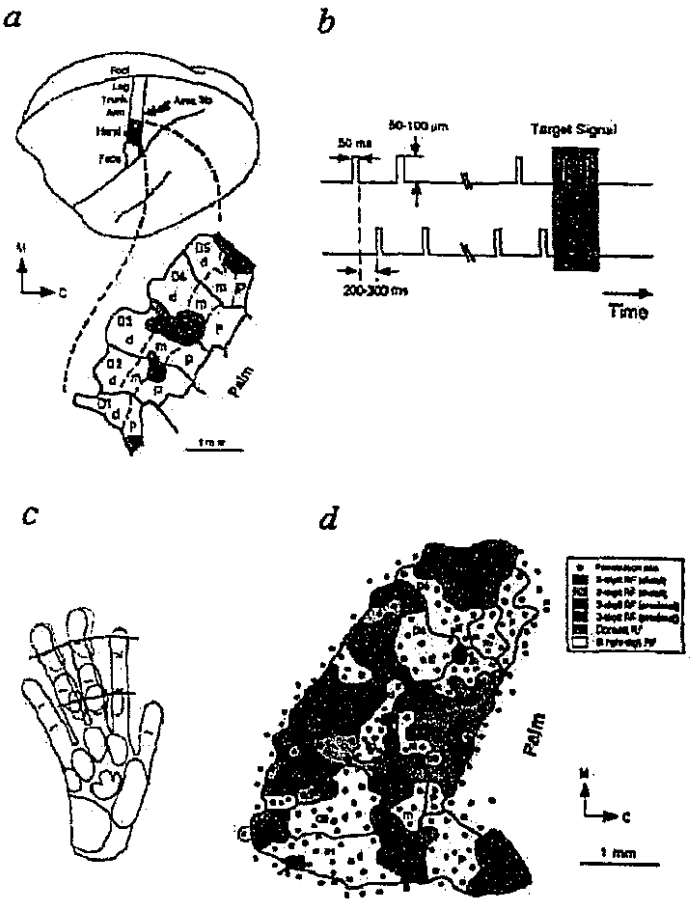

Fig. 7. Panel A shows a normal hand area representation in area 3b for a typical owl monkey. Somatotopy for the digits (1-5) as well as segmentation is indicated by proximal (p) middle (m) and distal (d) markers. Cortical zones representing dorsal hand surfaces are indicated by gray shading. Panel b shows the tactile stimulus sequence including a target interval. Finger tip stimulation is shown in the upper trace and finger base stimulation in the lower trace of panel B. Panel c shows the approximate location of stimulus skin contact. Panel d shows a typical reorganized map following training. Pink and red receptive fields indicate 2 and 3 digit receptive fields for distal skin segments respectively, while blue and dark blue regions indicate 2 and 3 digit receptive fields for proximal skin segments respectively. Coloured regions and gray shaded regions represent fusion and segregation effects respectively. From Wang et al. 1995.

Electrophysiological mapping of the ventroposterior nucleus of the thalamus showed normal single digit receptive fields.

Spengler et al. (1997) used the training procedure of Wang et al. (1995) to investigate whether the reorganization observed in monkey somatosensory cortex could be observed non-invasively in adult humans. Training consisted of 100-300 hits per session, using an identical apparatus and stimulus paradigm as in Wang et al. (1995), for 3 to 5 sessions per week for 3 to 4 weeks. Neuromagnetic responses evoked by 2 Hz pneumatic stimulation of the proximal, middle or distal phalanges of digits 2, 3 and 5 were recorded before and after the training series. Spengler et al. (1997) reported a significant decrease in the strength of current dipoles fitted to the P50 component, even though performance improved on the behavioural task. Dipole strength is thought to be an indicator of the net strength of cortical polarization which reflects the total number of synchronously firing neurons contributing to the cortical response (Williamson and Kaufman, 1990). Spengler et al. therefore concluded that the decrease in dipole moment was the result of a decrease in the neuronal population contributing to the evoked magnetic response, or fewer neurons firing synchronously. The authors could not reconcile their findings with those of Wang et al. (1995) which showed an increase in cortical territory representing the trained digits (fusion). Possible reasons for these discrepant findings are discussed in Chapter 5 of this thesis.

Mechanisms of Plasticity

In the experiments described above on remodeling of sensory representations by behavioral training, cortical reorganization was detected by measuring cortical representations in a context (typically anesthesia) substantially different from that

experienced during behavioral training itself. Because the changes persisted beyond training and were documented in a novel context, it is likely that alterations of synaptic efficacy by neuroplastic mechanisms was the basis of the measured effects. However, experiments by Braun & Wilms et al. (2000) and Braun & Schweizer et al. (2000) described earlier indicate that somatotopic representations may also be rapidly modulated by changes in the training context. In addition, it appears that somatotopic maps are rapidly modulated by attention. Noppeney et al. (1999) showed that the cortical distance separating magnetic dipoles representing digits 1 and 5 in one cerebral hemisphere depended on whether subjects allocated attention to stimuli delivered to that hemisphere. Much evidence reviewed recently by Buonomono & Merzenich (1998) suggests that attentional modulation of sensory representations is necessary for remodeling of these representations by behavioral training. Recently, Dykes (1997) detailed the hypothetical mechanisms that may govern neuronal plasticity in somatosensory cortex. Dykes (1997) describes the organization of somatosensory cortex as a dynamic equilibrium punctuated by relatively rapid shifts from one equilibrium to another. The conditions required to allow for sustained changes in organization are (I) a *permissive state* including prolonged excitation through disinhibition and the release of the neuromodulator acetylcholine (ACh) and (II) a *forcing function* in the form of an altered pattern of afferent input (Dykes, 1997).

Dykes describes the permissive state as a change in the balance of excitation and inhibition to favor prolonged depolarization of cortical neurons which is sufficient to open NMDA channels and favour calcium influx. The key function of the permissive state is an increased release of ACh and a decrease in inhibition (Dykes, 1997). One

noted effect of ACh release in somatosensory cortex is to act upon muscarinic receptors, which may result in potassium channels closing, thus broadening the action potential and allowing the NMDA channels time to open and trigger the cascade of events that leads to long term potentiation (LTP) (Dykes, 1997). Dykes (1997) suggests that these neural changes observed during the permissive state can be attributed to neuronal activity in the basal forbrain. Specifically, Dykes (1997) points out that basal forbrain activation simultaneously increases ACh release and reduce GABAergic inhibition. If a new pattern of input is presented during activation of the basal forbrain, a new receptive field will form, and remain and be maintained after the permissive state has ended.

Evidence for the role of ACh in somatosensory plasticity has come from a variety of sources. Dykes & Lamour (1988) have demonstrated that rat somatosensory neurons which lacked a receptive field to a cutaneous stimulus would develop one if the cortex was treated with ACh while the cell was activated by cutaneous stimuli. Another powerful demonstration of the role of ACh in behavioural learning came from Butt et al., (1997), who showed that ACh is released from somatosensory cortex during expectation and consumption of a food reward, and further, that ACh release was greatest during conditions that required learning a somatosensory discrimination to obtain the reward. Microdialysis probes placed in visual and somatosensory cortex (Jimenez-Capdeville et al., 1997) have also shown that stimulation of the basal forbrain can increase ACh by more than 500% in somatosensory cortex while producing only negligible changes in visual cortex, further implicating the basal forbrain as one controlling mechanism in the expression of ACh in somatosensory cortex.

Dykes predicts that basal forbrain activation will also release large numbers of cells from GABAergic inhibitory control. Anatomical evidence from Freund and Gulyas (1991) have reported that 68.5% of the targets of GABAergic basal forbrain axons were cortical GABA-containing interneurons. The activation of GABAergic basal forbrain neurons was therefore described as a means to disinhibit cortical pyramidal cells (Freund & Gulyas, 1991). While the role of the basal forbrain function in somatosensory plasticity continues to be considered, the plasticity model described by Dykes (1997) is, in principle, consistent with the observations of Jenkins et al. (1990) and Recanzone et al.(1992), which demonstrate that attention, reward and the presentation of new patterns correlated input appear to be important factors for the initiation of reorganization of adult primate somatosensory cortex.

Conclusion

This chapter has reviewed the literature on the somatosensory system of primates, including the specific tuning of cutaneous skin organs responsible for tactile sensations and their projections to somatosensory cortex. It then reviewed somatosensory evoked potentials (transient and steady-state) and how transient SEPs have been used to measure somatotopy by dipole analysis. A major conclusion of this review was that somatotopy can be detected noninvasively in humans through application of dipole analysis to EEG and MEG signals. However, measurement sessions have typically been lengthy, which is a limitation for studying the short term temporal dynamics of somatotopic maps by noninvasive procedures. In addition, previous mapping of digit somatotopy with EEG and mechanical stimuli had not been done at the time this thesis commenced. This was the goal of Experiment 1 to be reported in the next chapter (chapter 3), which also

compared EEG representations with those measured by MEG in the same subjects. Experiment 2, presented in chapter 4, employed steady-state procedures for somatotopic mapping and evaluated their relation to maps determined with transient stimulation and their stability over repeated sessions.

Chapter 2 also reviewed growing evidence from animal studies indicating that somatosensory representations in the primary somatosensory cortex are not statically fixed in the adult brain but are dynamically modulated by attention, context, and neural plasticity. The concluding experiment reported in this thesis (Experiment 3, chapter 5) extended our mapping procedures to investigate fusion and segregation of digit representations by behavioral training in human subjects.

Chapter 3

Somatotopic Organization of Human Somatosensory Cortex: A Comparison of EEG, MEG and fMRI Methods

Preview

In chapter 2 I pointed out that at the time of inception of the thesis, the generators of the mechanically evoked P50 had not been localized from EEG data. This experiment was undertaken to determine the cortical sources of this response. A second unique aspect of the study is that I obtained EEG and MEG measurements on the same subjects, so that MEG and EEG localizations could be compared. This was the first and presently the only paper in the literature to localize the generators of EEG and MEG somatosensory evoked potentials in the same individuals.

A third unique aspect is that we attempted to confirm our EEG and MEG source localizations by taking fMRI measurements on the subjects. We did not observe a significant fMRI activation to our tactile stimuli, both transient (3 Hz) and steady-state (18 Hz). We were able to confirm, however, that active finger flexion produces a robust fMRI signal in motor cortex (area 4) and in the postcentral gyrus, and that passive flexion which stimulates the proprioceptors without motor activity also activates the post-central region. These fMRI findings were novel but I did not pursue them further in the thesis.

I conducted the EEG and fMRI studies at McMaster University and the MEG measurements at C.T.F. Systems in Port Coquitlam, B.C. MEG measurements were supervised by D. Cheyne of Simon Fraser University. Drs. Cheyne, Roberts, and I collaborated on the manuscript. The paper appeared in Y. Koga, K. Nagata and K. Hirata (Eds.) Brain Topography Today, (1998).

Brain Topography Today.
Y. Koga, K. Nagata and K. Hirata, editors.

Somatotopic organization of human somatosensory cortex: a comparison of EEG, MEG and fMRI methods

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Abstract. *Background.* This study is an attempt to combine and compare EEG, MEG and functional magnetic resonance imaging (fMRI) methods to map the somatotopic organization of primary somatosensory cortex.

Methods. 32-channel EEG and 143-channel MEG recordings were acquired from two subjects during tactile stimulation of the fingertips. In addition, fMRI activation maps were produced during fingertip vibration and finger movements. Dipole analysis was used to calculate source location and confidence regions for the EEG and MEG responses which were compared to the fMRI activation maps.

Results. The 50 ms response in the averaged EEG and MEG data could be modeled as an equivalent current dipole in the postcentral gyrus with the expected somatotopic organization. 95% confidence regions indicated that sources for individual digits can be discriminated with sufficient signal-to-noise ratio.

Conclusions. The results indicated that the somatotopic organization of the somatosensory cortex can be successfully demonstrated using EEG and MEG responses to mechanical stimulation of individual digits. Initial fMRI results suggest that tactile stimulation does not produce robust responses, whereas passive stimulation produced clear activation patterns in the postcentral gyrus in close proximity to the dipole sources for tactile stimulation.

Keywords: dipole source analysis, functional neuroimaging, mechanoreceptors, somatotopy.

Introduction

One of the recent advances in human neuroscience has been the development of noninvasive functional imaging techniques which allow the precise localization of brain activity associated with simple sensory and motor processes. Many recent studies have attempted to combine these various methodologies, both for the purpose of cross-validation of different experimental techniques, and in order to obtain more information about human brain function than may be derived from any method alone. In order to achieve this goal, however, it is necessary to establish methods for the precise combination of these techniques and to test

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these methods using well-understood neurophysiological phenomena.

It has been shown in previous studies that evoked responses can be elicited by mechanical stimulation of the fingertips. In contrast to responses evoked by electrical stimulation, the earliest large response evoked by tactile stimulation occurs at a latency of about 50 ms, labeled the P50 and P50m in the EEG and MEG, respectively [1–3]. In theory, MEG and EEG measure orthogonal patterns of electric potential and magnetic flux at the scalp surface produced by simple current sources. The observed orthogonality of the respective topographies of the P50 response therefore makes this an ideal component for the comparison of EEG and MEG source modeling methods. In this study, we attempted to map the somatotopic organization of individual fingers in the postcentral gyrus using dipole source analysis applied separately to EEG and MEG evoked responses under similar stimulus conditions in the same subjects. In addition, we attempted to compare these electrophysiological responses to local blood oxygen level dependent (BOLD) changes as indexed by fMRI of the sensorimotor area during vibration of the fingertips, as well as active and passive movements of the same digits.

Methods

High-density EEG recordings were obtained from a grid of 19 electrodes overlying the left sensorimotor area, in addition to 13 distributed electrode sites using a 32-channel EEG system (Neuro Scan Inc) in two subjects. In a separate recording session, whole-head MEG measurements were made using a 143-channel biomagnetometer system (CTF Systems Inc). Stimuli consisted of 5-ms duration pulses applied to the tips of the first, third and fifth digits of the right hand at an interstimulus interval of 750 ms, which produced a light tapping sensation. MEG recordings were obtained in an unshielded environment using software-constructed third-order gradients to reduce background environmental noise [4]. In addition, fMRI data were collected using a GE Signa 1.5T scanner and a spiral sequence (four spirals, TE/TR = 35/640 ms, flip angle = 45°, FOV = 18 cm, in-plane resolution 2.8 mm, matrix 128 × 128) during 3- and 18-Hz vibration of the fingertip as well as active and passive finger movements. Up to eight contiguous, 4-mm thick axial slices were imaged at a slightly oblique angle passing through the sensorimotor region of both hemispheres. For the vibration condition, 10 trials each consisting of 23 s stimulation and 23 s rest were collected for each finger, with fingers fixed in place to prevent movement between and during scans. For the active and passive movement conditions, 2-cm flexions of the digit at 4 Hz were produced either by the same probe used to stimulate the fingertip (passive movement condition) or by the subject (active movement condition) for 18 s followed by 18 s of rest. T maps were created by the subtraction of control (rest) conditions from the activation periods (vibration or movement) after correction for in-plane motion artifacts, and then projected onto two-dimensional fast inversion-recovery (FIR) structural images obtained for each

activation slice. In addition, T1-weighted volumetric images were obtained from each subject for coordinate system matching and superposition of dipole sources on anatomical structure.

Single equivalent current dipole source locations were estimated for the P50m response using a spherical conductor model with corrections for nonradial field contributions and for software gradiometer formation. The sphere origin was based on the skull boundaries as shown in the structural MRI which was found to produce the lowest error (*cf.* [2]). EEG source analysis was achieved using a four-shell spherical model based on that of Stok [5] translated by the origin of the MEG sphere to obtain the dipole coordinates for MEG and EEG dipole fits to the same head-based coordinate system. In addition, Monte Carlo simulations were performed to obtain 95% confidence ellipsoid surfaces [6], using the average noise level of the prestimulus data which were projected onto the volumetric MRI images for each dipole source.

Results

Figure 1A shows representative waveforms for EEG and MEG responses to mechanical stimulation of the right thumb in one subject. The P50 and N70 responses can be seen clearly in the EEG data which correspond to a large field reversal at 50 ms in the MEG followed by a smaller reversal at 70 ms. As shown in Fig. 1B, both the EEG and MEG data show dipolar field reversals over the contralateral (left) central scalp at a latency of 50 ms (P50). These patterns were always dipolar with orthogonal orientations, suggesting a tangential anterior-posterior directed current source consistent with polarization of the wall of the postcentral gyrus. In contrast, a monopolar pattern was observed for the N70

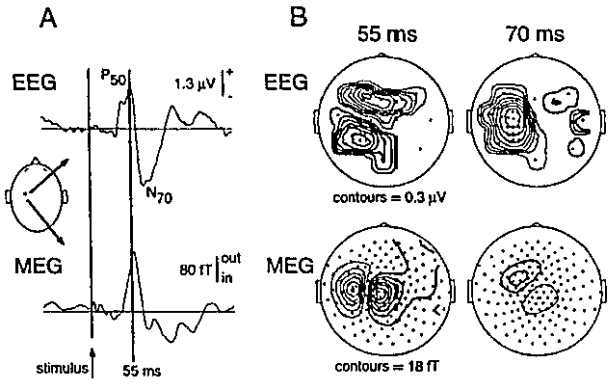

Fig. 1. **A:** EEG (top) and MEG (bottom) averaged responses for tactile stimulation in one subject, recorded over the left central scalp. Note the large response in both waveforms at approximately 55 ms. **B:** Vertex projection (nose upward) isocontour maps for EEG (top) and MEG (bottom) at 55 and 70 ms latencies. Thick contours indicate positive potential and ingoing flux, and thin contours indicate negative potential and outgoing flux.

with a weak or absent response in the MEG suggesting a predominantly radially oriented source.

Dipole locations showed similar locations for both the P50 and P50m with a somatotopic distribution along the postcentral gyrus for different digits as shown for the EEG sources in one subject in Fig. 2. Average separation between first and fifth digits for both MEG and EEG dipoles in both subjects was approximately 6 mm and 95% confidence regions calculated for each source indicated maximum localization errors ranging from 3 to 8 mm, these values being highly dependent on response amplitude which varied across subjects and different fingers. Thus, for cases where response amplitudes were sufficiently large, the 95% confidence regions of the sources for individual digits could be clearly separated. Discrepancies between dipole locations for MEG and EEG did not reflect an overall constant error in coordinate system translation, but rather variability of dipole location for each method alone.

For the analysis of the fMRI data, images for stimulation and rest (baseline) conditions were corrected for in-plane motion and then subtracted to produce T test maps for each finger condition. These images were projected onto the appropriate FIR anatomical image. In the subjects tested, no significant activation patterns were observed for 3- or 18-Hz finger vibration in the region of the postcentral gyrus. However, passive flexions of a single digit showed focal activation in the region of the hand area of postcentral gyrus (Fig. 3, right), whereas voluntary finger movements of the same digit showed increased activation in both pre- and postcentral cortex (Fig. 3, left).

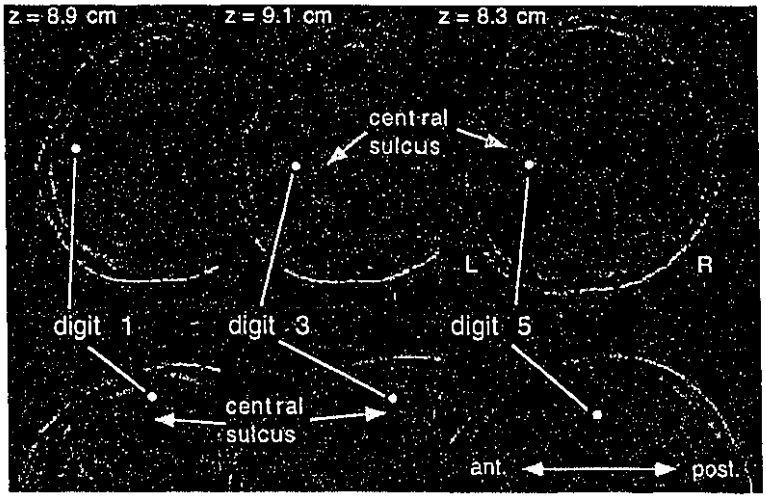

Fig. 2. Dipole source locations projected onto T1-weighted axial (upper) and sagittal (lower) MRI slices for the first, third and fifth digit stimulation conditions. Note that the source for digit 5 is medial but inferior to the source for digit 1.

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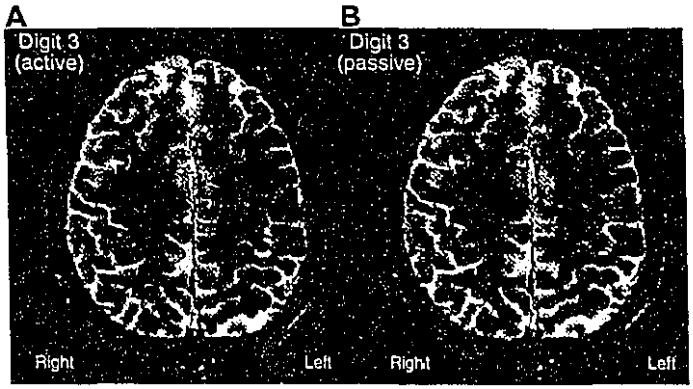

Fig. 3. T maps produced by subtraction of rest from activation conditions projected onto fast inversion recovery MRI slices for active third digit flexion (left panel) and passive third digit flexion (right panel) conditions in the same subject. Areas of significant activation are shown as white areas outlined in black and correspond to T values exceeding 6.0 (left panel) or 4.5 (right panel) where $p < 0.001$.

Discussion

The results of this study indicated that the somatotopic organization of the somatosensory cortex can be successfully demonstrated using EEG and MEG responses to mechanical stimulation of individual digits. Overall separation for digits of the hand was about 6 mm which is consistent with the observations of Buchner et al. [7], who were able to model the N20-P20 evoked response to electrical digit stimulation as a tangential source in SI. In our study, source locations projected onto a region of the postcentral gyrus are immediately posterior to the hand region of the precentral gyrus as identified by anatomical landmarks [8]. Remaining discrepancies between EEG and MEG results may indicate separate sources of error for each method, such as head movement, errors in projection of electrode position and differences in sampling density (32 EEG vs. 143 MEG), or errors introduced by the use of a spherical conductor model. Further studies are required to identify and eliminate these remaining sources of error.

Our initial fMRI results indicated that tactile stimulation does not produce robust activation patterns in SI, making it difficult to compare metabolic changes to tactile stimulation with dipole source locations. Passive finger flexions most likely activate different neuronal populations in SI (i.e., neurons receiving proprioceptive input located in Brodmann's area 3a in comparison to those neurons receiving input from mechanoreceptors in area 3b). Thus, passive movement of the fingers may reflect cortical responses related to proprioceptive feedback from muscle stretch receptors in the forearm, as opposed to the receptive fields in the hand (*cf.* [9]). Nevertheless, the fMRI T maps indicated activation in the postcentral gyrus during passive finger flexions in close proximity to dipole sources for tactile stimulation. It is interesting that a similar region in the post-

central gyrus shows activation during active movements of the same finger. This is similar to the results reported by Gerloff et al. [10] and supports recent evidence that sensory feedback during voluntary movements involves input from muscle stretch receptors in the periphery to SI [11] which may also be elicited during passive finger movements. Whether these responses will also show somatotopic organization similar to that for tactile stimulation requires further study.

Acknowledgements

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Chapter 4

Comparison of the Cortical Sources of Steady State and Transient Responses Evoked by Mechanical Stimulation of the Fingers

Preview

Experiment 1 (Chapter 3) showed that we can measure somatotopy with EEG using transient mechanical stimulation. However, the measurement procedure was lengthy, requiring a total of 60 minutes of transient stimulation for 3 digits (20 min per digit). Because maps were determined only once, their repeatability is not known.

The purpose of Experiment 2 was to assess somatotopy using steady-state stimulation, which may measure somatotopic representations more efficiently. We compared maps determined from steady state SEPs (18 Hz stimulation) with those determined from transient SEPs (3.1 Hz stimulation), in the same subjects. In addition, maps were repeated five times over a period of 5 weeks, to assess their stability. I present the study as a pre-submission publication draft. For convenience, the figures are presented at the end of the chapter.

Comparison of the cortical sources of steady state and transient responses evoked by mechanical stimulation of the fingers

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Penfield and Bouldry (1937) were the first to describe somatotopic maps of the human body surface in postcentral cortex. Somatotopic maps were determined from verbal reports given by patients of the sensations they experienced when the exposed cortical surface was stimulated during surgery for intractable epilepsy. Within the cortical hand area, which was found in the posterior bank of postcentral gyrus, the representation of the little finger was reported to be medial and superior to that of the thumb with intermediate digits falling between these sites in a medial to lateral plane. These observations were later confirmed by recording somatosensory evoked potentials (SEPs) from electrodes placed directly on the somatosensory cortex (eg. Woolsey et al., 1979; Wood et al., 1988; Allison et al., 1989; Baumgartner et al., 1993). Intracortical mapping, however, cannot be used for studies of the dynamics of somatosensory processing in normal subject populations.

A more recent approach has been to measure electrical or neuromagnetic fields evoked by somatosensory stimulation using dense sensor arrays positioned over the scalp of intact subjects. Magnetic or electrical source imaging (dipole analysis) is subsequently applied to localize the cortical generators of the evoked field and to superimpose these sources on neuroanatomy measured by MRI. Using these techniques, somatotopy has been documented for several latency components of electrical and magnetic field patterns evoked by electrical, tactile, and pneumatic stimuli (Buchner et al., 1995; Braun et al., 1999; Elbert et al., 1995). Without exception, these studies have employed low frequency stimulation (typically <3 Hz) to evoke "transient" brain responses that subside between successive stimulus events. A limitation of this procedure is that somatotopic mapping requires lengthy measurement times (typically about an hour for a mapping of three digits) that limit the study of somatosensory dynamics.

If the interval between stimuli is shortened such that successive brain responses begin to overlap, the stimulus procedure is referred to as a "steady state" procedure, and the observed response as a "steady state" response (Regan, 1982). Steady state procedures may offer some advantages for somatotopic mapping. Data are acquired rapidly, and because stimulus-locked brain activity can be separated from other brain responses by band pass filtering or in the frequency domain, the signal to noise ratio may be improved. In principle, multiple fingers could be simulated simultaneously, each at a different stimulus repetition rate, and the corresponding representations separated in the frequency domain. In a linear system, transient and steady-state responses should provide alternative pictures of the same phenomenon. In such a system the time-domain average of the steady state response should be given by a linear summation of transient

evoked responses at their characteristic latencies. However, the assumption of linearity is debated for steady state responses of the auditory (Galambos 1981, Gutschalk et al., 1999, Pantev, 1996) and visual systems (Regan, 1980, Muller et al., 1997). Little information is available comparing transient and steady-state responses in the somatosensory system.

In the experiment reported in this paper, high resolution EEG was used to evaluate somatotopic representations evoked by steady state mechanical stimulation of the fingers in human subjects. One goal was to determine whether somatotopy can be detected with this method, and to determine whether somatotopic maps are reproducible over sessions. A second goal was to compare somatotopic maps measured from steady-state responses with maps based on transient responses. We determined whether the two maps gave similar pictures of somatotopy, whether they were equally repeatable over sessions, and contrasted their measurement times.

Methods

Subjects

Five healthy right handed male subjects (age 24-30) gave their informed consent in accordance with the Declaration of Helsinki and were paid for their participation. Each subject participated in 5 repeated mapping sessions which were separated by about 1 week on average (mean: 7.8 days, minimum of 3 days and maximum of 15 days).

Procedure

Mechanical stimulation of the fingertip was generated by a single digit stimulator constructed of a solenoid attached to a teflon rod with a rounded tip that delivered tactile stimulation to a skin area of approximately 2 mm^2. The teflon rod was centered inside an 18" long 4 mm diameter hard plastic cylinder, where the opening from one end made contact with the skin surface encircling the site of stimulation. This design was used to stabilize contact with the skin and to limit the spread of vibration on the skin surface (Bolanowski et al., 1988). To ensure that the stimulation was limited to the same location on the fingertip over repeated measurement sessions, finger position was controlled with a wooden 'horseshoe' that limited the distal and mediolateral movement of the finger (see Figure 1). Subjects were asked to find a relaxed arm and hand position prior to each recording session. Arm and hand rests were mechanically isolated from the stimulation device to prevent the spread of flutter sensation to the hand and forearm. The stimulator solenoid was housed in a sound-attenuating and electrically shielded case to reduce acoustic and electromagnetic artefact. Residual acoustic artifacts from the stimulator were masked with ear plugs and low-level white noise presented over head phones.

Figure 1 about here

Subjects were seated comfortably in a dimly lit, electromagnetically shielded room, with one finger of the right hand positioned on the stimulator. A computer generated visual display cued the subjects to position a designated finger (digit 1, 3, or 5) on the stimulator and provided a visual fixation point once stimulation of the digit

commenced. The stimuli were delivered in the same way for each subject and each recording session. Two stimulus procedures were studied, each applied to digits 1, 3 and 5 of the right hand as described below.

Transient Stimulation (40 minutes). The somatosensory evoked response to tactile stimulation of the finger tip presented at long interstimulus intervals contains several components, the most prominent of which is a dipolar pattern showing a maximum frontal negativity and parietal positivity near 55 ms, termed variously the "P55" response (Hamalainen et al., 1994; Cheyne et al., 2000; Braun et al., 2000). This component has been localized to area 3b of somatosensory cortex by neuromagnetic investigations (Suk et al., 1991; Yang et al., 1993; Cheyne et al., 1998; Elbert et al., 1995; Braun et al, 1999). In pilot studies we observed little diminution in the amplitude of this component of the transient response up to stimulation repetition rates of 3 Hz. Therefore, in order to gather as much data as possible for measurement of the transient somatotopic map, 3 Hz (3.1 Hz by actual measurement) was chosen as the repetition rate for the transient stimulation.

Transient responses were evoked by presenting 5 minute trains of 3.1 Hz stimulation first to digit 1, followed by digit 3 and then digit 5. A brief rest period was permitted between 5 minute blocks. This series was then repeated for a total of 2 five minute blocks of 3.1 Hz stimulation for each digit (1860 repetitions in total). Prior to these measurements, stimulator artefact was assessed by recording the EEG for a single block of 5 minute duration while the stimulator was operated but the subject's finger was removed from the stimulus probe. The total time required for measurement of the transient response and artefact was about 40 minutes.

Steady-state Stimulation (20 minutes). Steady state responses arising from linear superimposition of transient components will reach their amplitude maximum when the steady state stimulation rate is chosen such that the constituent transient responses are aligned in phase. The optimal rate of steady state stimulation for visualization of a transient response with a latency near 55 ms would be expected to be near 18 Hz. We chose this rate for determination of the steady state somatotopic map. Measurements taken in our laboratory and recent findings by Tobimatsu et al., (1999) indicate that somatosensory steady state responses reach their amplitude maxima between about 18-25 Hz.

Steady state measurements were initiated after completion of transient measurements. First, stimulus artefact was assessed by delivering 5 minutes of 18 Hz stimulation with the subject's finger removed from the tactile probe. Digits 1, 3, and 5 were then stimulated at 18 Hz in consecutive 5 minute blocks with digit 1 stimulus first, followed by digit 3 and then digit 5. Within each 5 minute block each digit was stimulated 5400 times.

Prior to conducting this experiment, a calibration study was conducted on two subjects in order to match the subjective intensity of the 3.1 Hz pulse to that of 18 Hz. pulse trains. Due to the operating characteristics of the solenoid, stimulus intensity varied directly with stimulus duration. The 3.1 Hz tactile stimulus set at 10.75 ms duration produced a moderate tapping sensation. The psychophysical line of subjective equality for a 3.1 Hz standard stimulus at 10.75 ms duration was determined for 18 Hz stimuli to be 9.5 ms.

EEG recording and analysis

Prior to each mapping session, 3 dimensional electrode positions and fiduciary landmarks (nasion, preauricular left and right landmarks) were recorded for each subject (Polhemus Inc.). A 64 channel EEG system (Neuroscan) was used to record electrical potentials (low-pass filtered between DC and 100 Hz, with and A/D rate of 500 Hz). The 64 scalp positions included sites from the 10-20 system as well as a concentration of electrodes over the contralateral central sulcus (see Figure 2). EEG was recorded continuously with electrode Cz as a reference and was re-referenced off-line using a common average reference. Both transient and steady-state data were epoched off-line (including noise measurements) into epochs of 416 ms duration (144 ms pre-stimulus) and averaged over each delivered stimulus. Epochs contaminated by eye movements and movement artefact (changes > than 100 mV at any electrode) were rejected from further analysis. Transient data were band-pass filtered at 3-50 Hz (FIR filter, zero phase shift) and base-lined to a 144 ms pre-stimulus period. Each of the two 5 minute blocks of 3.1 Hz stimuli were averaged together for each digit to produce a grand average with a maximum of 1860 repetitions of 3.1 Hz stimuli. Steady-state data were band-pass filtered at 15-21 Hz (FIR filter, zero phase shift) and base-lined over the entire 416 ms period. This filter setting was used to select the fundamental frequency (18 Hz). All 18 Hz stimuli within the 5 minute block were averaged to include a maximum of 5400 stimuli per digit.

Dipole analysis

The 5 minute noise measurements for transient and steady-state stimulation were observed to contain negligible (<0.1μV peak to peak) electromagnetic artefact resulting from the operation of the stimulus at either 3.1 Hz of 18 Hz. The noise measurements were not analyzed further.

Figure 1 about here

Dipole analysis was performed with the single dipole method of Cheyne et al. (1998) which was based on an approximated three-shell spherical head model. Dipole analysis for 3.1 Hz stimuli was performed on the P55 component and was initiated by a single dipole positioned in the approximate area of contralateral somatosensory cortex. Dipole solutions were determined for each time point between 40 ms and 80 ms (20 solutions in total) and RMS values were calculated. Dipole solutions for the transient response were calculated as the average of 5 contiguous solutions spanning the peak RMS. Similarly, the dipole analysis procedure for steady-state response involved the analysis of each time-point between 10 ms and 30 ms. The peak RMS was recorded and the average of the five time-points around the peak RMS value was calculated. Dipole solutions consisting of position, orientation, strength and residual variance were recorded for each stimulus condition. Following Buchner et al. (1995) dipole solutions were re-determined after a regional source was fitted to remove brain activity over the interval 20-40 ms preceding the P55 component. This approach did not yield more stable solutions and will not be described further.

Typically, dipole analysis involves the exclusion of data that does not conform well to the dipole model, ie. where high residual variance (>10%) is observed. In such

cases, the data and often the subject are removed from further analysis. In this experiment, data for each subject and session were necessary to describe the repeatability of somatotopic representations. Thus, all dipole solutions were initially accepted to give a complete set of observations, without imposing any constraints on residual variance or spatial position. These 'raw' dipole solutions were then compared to the same set after imposing constraints on the observed solutions. The dipole constraint criteria were a residual variance no greater than 15% and a dipole location at least 4 cm superior to the preauricular axis (a line extending between the preauricular points located approximately 1 cm anterior to the opening of the auditory canal) in the contralateral hemisphere.

Volumetric magnetic resonance images were recorded for 1 subject (Subject 1). A T-1 weighted image MRI was obtained (G.E. Medical Systems, 1.5 Testla) using 124 sequential sagittal slices of 1.5 mm thickness, with a resolution of 256 X 256 points on a field of view of 240 X 240 mm. Co-registration of EEG dipole sources with the volumetric MRI was performed by matching fiducial markers (nasion and pre-auricular points) with electrodes to fiducial points in the MRI for the same subject, which resulted in a common head coordinate system for EEG dipole solutions and the structural brain image.

Results

Transient and steady-state responses from one subject and a single session are shown in Figure 2. A polarity reversal is observed in the average trace for both transient and steady-state responses. The topographic map for the peak amplitude of the response is also shown in Figure 2, at the time point indicated by the vertical line. Transient mechanical stimuli presented to the digits evoked a P55 response for each stimulated digit for all subjects. The steady-state response showed a dipolar pattern reversing in polarity during each cycle of the steady-state stimulus (every 54 ms). The amplitude for the P55 response averaged over all 5 subjects and digits was 1.58 μV (peak to peak) with an average latency of 55.52 ms. By contrast, the average steady-state response over all digits and sessions was 0.59 μV (peak to peak).

Figures 2, 3, and 4 about here

Figure 3a shows the dipole positions obtained at 3.1 Hz and 18 Hz for each digit for Subject 1 (the same subject as in Figure 2) averaged over five sessions. A Penfield-like somatotopy was observed with digit 5 lying medial and superior with respect to digit 1 in both maps (3.1 Hz and 18 Hz), with little difference between the two mapping conditions. Dipole positions differed significantly among the three digits in the inferior-superior coordinate for this subject, $F(2,8)=8.4419$, $p=0.011$, and approached significance for the mediolateral coordinate ($p= 0.68$) with no effect attributable to mapping procedure (transient or steady-state). Dipole positions (average of five sessions) are co-registered on the subject's MRI in Figure 4. The obtained positions in the coronal section are broadly consistent with cortical sources situated in primary somatosensory area 3b, although in the anterior-posterior axis they fall anterior to area 3b where the generators are expected to reside.

In order to illustrate the variability obtained between sessions, solutions obtained for each individual session are shown for digits 1 and 5 in Figure 3b, together with average over sessions repeated from Figure 3a. There was some spread of solutions for digit 1 into those of digit 5 along the lateral-to-medial axis, while solutions for digit 5 tended to cluster somewhat more closely in the medial/lateral quadrant. This was true for the 3.1 Hz as well as the 18 Hz maps. In this subject the two most distant outliers were from the 18 Hz condition.

Somatotopic maps determined for each subject and stimulus condition (3.1 Hz and 18 Hz) averaging over sessions are given in Figure 5, where for purposes of comparison the results for Subject 1 are repeated. Maps shown on the left were determined from all available data, whereas maps presented on the right show the effect of imposing residual variance and anatomical constraints on dipole solutions. Inspection of these findings shows that with one exception (Subject 5, no criterion imposed) dipoles calculated for digit 5 were located superior and in most cases medial with respect to solutions for digits 1 and 3. However, the distance between digit representations was greater for subjects 1 and 2 than for the remaining subjects where clustering was observed. Statistical analyses carried out for each subject are summarized in Table 1. The main effect comparing dipole position among the stimulated digits without acceptance criteria was observed to be significant in 4 out of the 5 subjects in either the medial lateral coordinate or the inferior superior coordinate. The imposition of a residual variance criterion had little effect for all but one subject (subject 5). Inspection of Table 2 indicates that this subject showed the largest residual variances of the group, frequently exceeding the 15% criterion particularly in the 3.1 Hz condition. This subject is the only case where the 3.1 Hz and 18 Hz maps were statistically differentiable, with $F(1,4)=85.45$ and 22.4 for the inferior-superior and medial-lateral coordinates, respectively, in the no-criterion condition (Table 1). In this subject, and also in Subject 2, the 18 Hz steady-state map tended to be medial with respect to the 3.1 Hz transient map.

Figure 5 and Tables 1 and 2 about here

Mean dipole position (x, y, and z coordinates) across the five sessions is reported for each subject in Table 3 where all available data are used (no acceptance criteria imposed). The stability of dipole solutions was quantified by calculating the standard deviation over the 5 repeated measurements for each subject, and averaging these across subjects and digits for the 3.1 Hz and 18 Hz conditions, separately. The mean standard deviation of dipole positions obtained for the 3.1 Hz condition (0.59 mm) was smaller than obtained for the 18 Hz condition (0.68 mm), but this difference did not reach significance. Mean residual variances are also shown in the bottom row of Table 3 separately for each digit and stimulus condition, averaged across subjects. Residual variances tended to be lower when stimulation was presented at 18 Hz, but this difference, too, was not significant. Dipole moment averaged over sessions is presented for each subject and digit in Table 4, separately for the 3.1 Hz and 18 Hz stimulus frequencies. Consistent with signal amplitude measurements, dipole moments observed for 3.1 Hz stimulation (mean 3.89 nAm) were approximately twice as large as 18 Hz responses (mean 1.54 nAm) for all subjects and sessions, paired t-test $P<0.0001$.

Tables 3 and 4 about here

Discussion

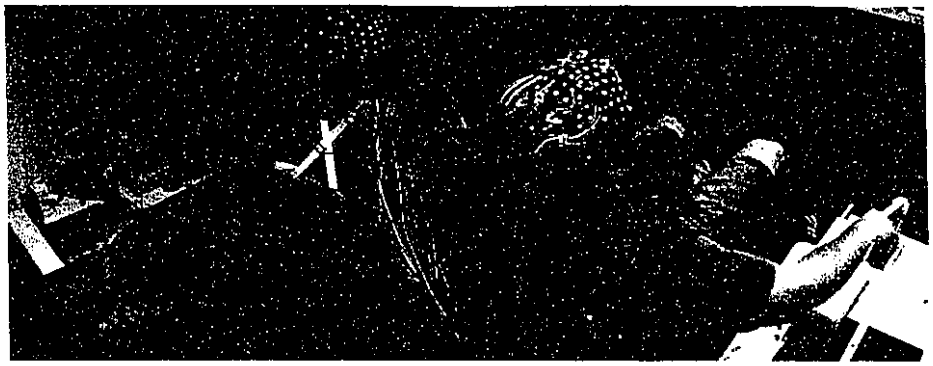
The principal aim of the present study was to compare the somatotopic maps observed with mechanical transient digit stimuli to somatotopic maps observed using a steady-state stimulus and to assess the repeatability of these representations. The results from this experiment were in agreement with previous work (Cheyne et al., 1998; Braun et al., 1999) which have shown that EEG responses to mechanical transient digit stimuli are somatotopic. Our results demonstrate that steady-state representations also showed a Penfield arrangement of the digits. Digit 1 was inferior and lateral to the superior medial digit 5 in 3 out of 5 subjects using a transient stimulus and 4 out of 5 subjects using steady state stimulation. The 3.1 Hz and 18 Hz maps were congruent with one another and could be statistically segregated only for one subject. The steady-state responses showed smaller dipole moments, but similar residual variance of the dipole fits and variability between days in the spatial coordinates of these fits compared to maps determined from transient responses. To our knowledge, these data are first to describe the repeated EEG measurements of somatotopic representations in humans using a mechanical steady-state stimulus.

A second aim of this experiment was to contrast the measurement times of the transient and steady state stimulus procedure. Steady-state maps were determined in half the measurement time than that of transient maps with similar precision. Each digit was mapped with 10 minutes of stimulation at 3.1 Hz and 5 minutes of stimulation at 18 Hz. Despite the difference in measurement time, transient and steady-state stimuli appeared to activate closely adjacent cortical regions of primary somatosensory area 3b in at least 4 of our 5 subjects. Regan noted (1982) that for all linear systems the transient response has a fixed linear relationship to the steady-state response and can be thought of as alternative formulations of the same data. While there is evidence that auditory and visual pathways show non-linear behaviour (Pantev et al.,1998), this experiment supports the assertion that transient and steady-state response in the somatosensory system are alternate formulations of the same basic sensory process. This conclusion is supported by a recent MEG experiment which compared single digit responses to several different steady-state frequencies ranging from 50 to 400 Hz. Hashimoto et al. (1998) observed no statistically significant differences to dipoles evoked by different frequencies of index finger stimulation.

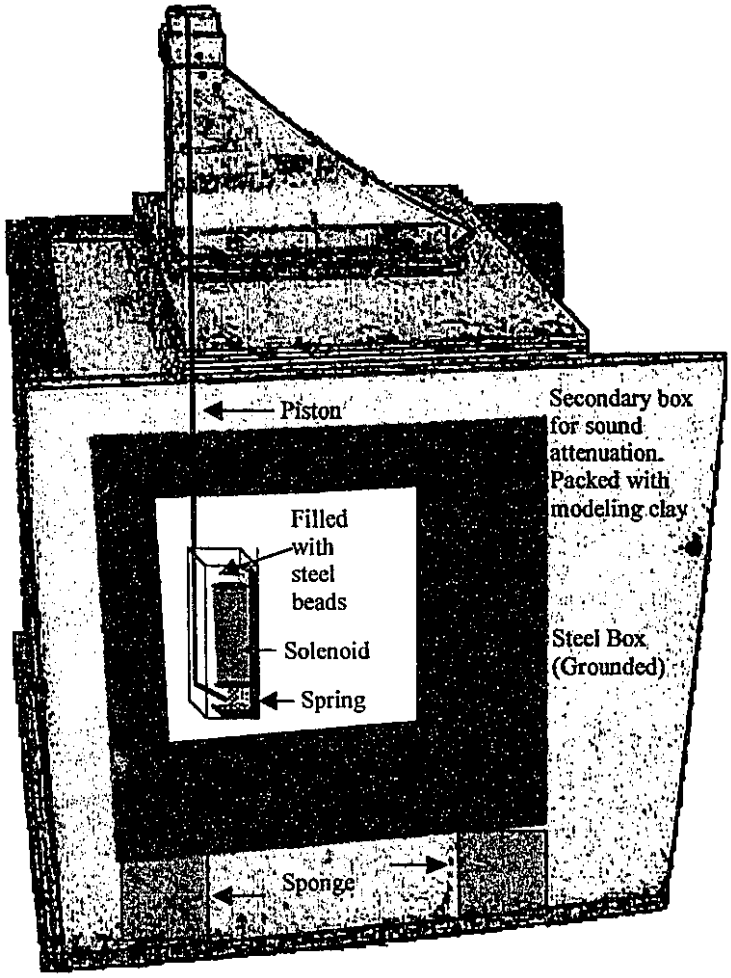
The somatotopic maps observed in this experiment showed a distributed representation of the digits for two subjects e.g Subjects 1 and 2, (Figure 5) and more compressed representations in the remaining 3 subjects. The addition of a regional dipole source to factor out activation of subcortical activity prior to the onset of the P55 component (as recommended for N20 median nerve solutions by Buchner et al., 1995) did not alter this picture. Although the absence of a prominent N20 in our study where mechanical stimulation was used could have limited the value of adding a regional source, it should be noted that previous mapping experiments have also described

variable somatotopic representations including interleaved digits and compressed representations (Baumgartner et al., 1993, Buchner et al., 1995). In our study we found that both types of maps (distributed and compressed) were repeatable over sessions. Repeatability of the dipole positions (without an acceptance criteria) measured as standard deviations among days in each spatial coordinate ranged between 5.84 mm to 7.14 mm. These results are within the range of values reported using median nerve stimulation by Buchner et al., (1995) where a 95% confidence interval was observed to be on the order of 5-6 mm for the localization of the tangential dipole of the median nerve N20 response. Coregistration of the dipole positions (averaged over sessions) onto one subject's MRI (Figure 4.) were observed anterior to known anatomical landmarks (Yousry et al., 1997) for the somatosensory and motor cortex. This was probably due to inadequacies in the coregistration of a spherical head model to the subjects MRI. Realistic head models may be needed to correct for such coregistration errors, as the relative placement of the electrodes to the subjects anatomy is preserved.

Steady-state stimulation may be advantageous for more efficiently determining somatotopic representations. Simultaneous presentation of several steady-state stimulus frequencies, each separately to a specific skin site, may further improve on the efficiency of somatotopic mapping. The feasibility of this approach is a question for future study.



1A.



1B.

Fig. 1. The above panel (Fig 1A.) shows the experimental apparatus during EEG data collection. Residual acoustic artifacts from the stimulus were masked with ear plugs as well as white noise presented over headphones. The electromechanical stimulus and housing are shown in the lower panel (Fig 1B). An electromechanical solenoid was used as the stimulus. Electromagnetic artifacts were reduced with ferrous shielding both around the solenoid (steel beads) and with an additional steel housing around the solenoid which was connected to ground. Attenuation of acoustic artifacts was aided by mounting the solenoid housing inside a larger box which was packed with modeling clay. Note that the arm rest in Fig 1A. is also mechanically isolated from the stimulus.

Subject 2, Digit 3:
3.1 Hz vs. 18 Hz

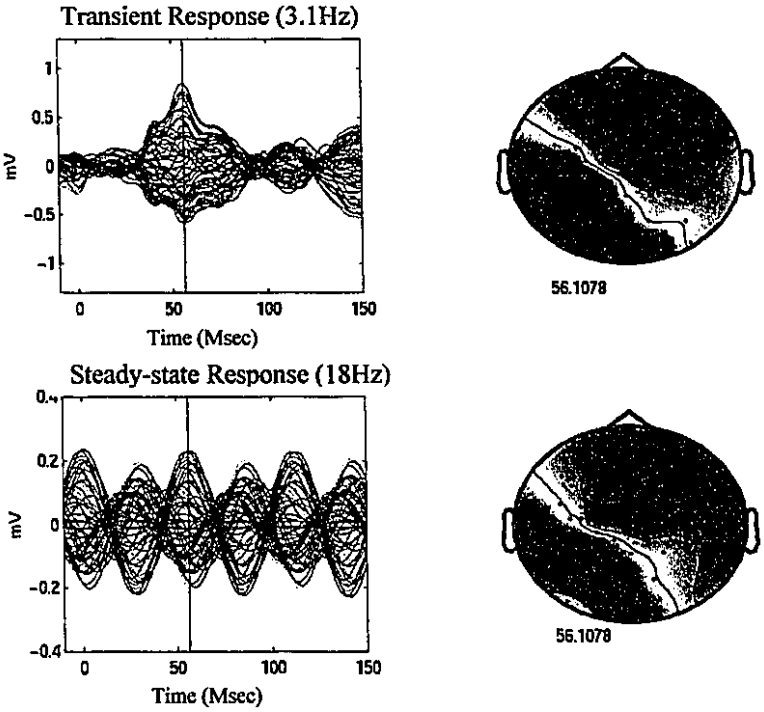


Fig. 2. Grand averaged 64 channel EEG traces for a Subject 2, digit (3) responses to 3.1 Hz and 18 Hz stimulation over 5 sessions. The cursor marks the maximum RMS time point of the dipolar reversal for each trace. The upper left trace shows the response to 3 Hz transient mechanical stimulation. Note the polarity reversal at the time point of maximum RMS. The bottom left trace shows the response to 18 Hz stimulation. The topographic maps show the electrical current distribution of the reversal at the time point of the cursor. Black dots on the topographic maps indicate electrode positions.

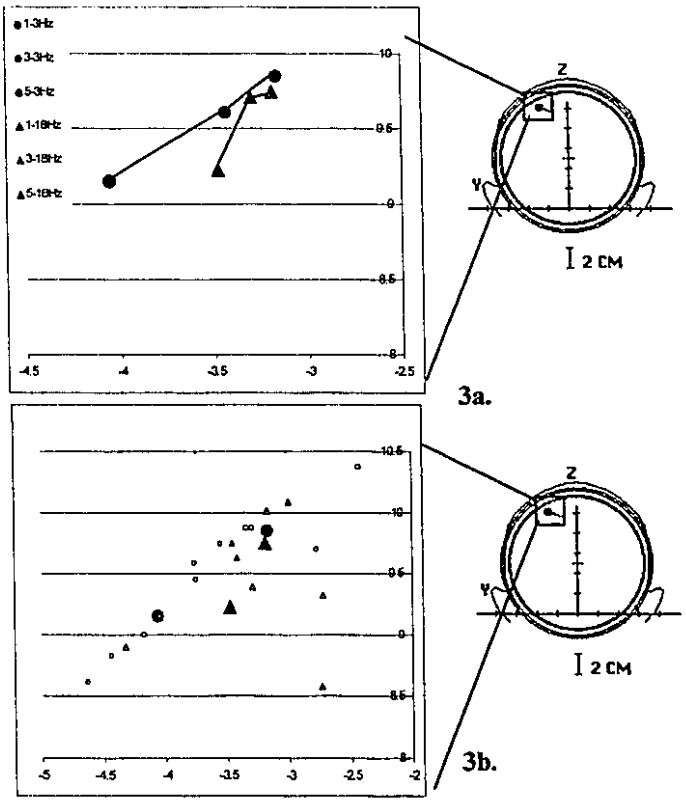


Fig. 3. Panel 3a shows the grand average of dipole positions observed for Subject 2 following 3.1 Hz and 18 Hz stimulation of digits 1, 3, and 5 (no acceptance criterion where all calculated positions are included). Dipole maps show *Penfield-like* somatotopy where digit 1 lateral and inferior to digit 3 and digit 5 for both 3.1 Hz and 18 Hz representations. Panel 3b shows all dipole positions for digits 1 and 5 which make up the grand average in 3a. The large blue circle (Digit 1 at 3.1 Hz) is the average of the 5 small blue circles from each session. The large red circle (Digit 5 at 3.1 Hz) is the average of the 5 small red circles from each session. Responses from 18 Hz stimulation are similarly shown as triangles. Digits 3 responses were omitted for clarity.

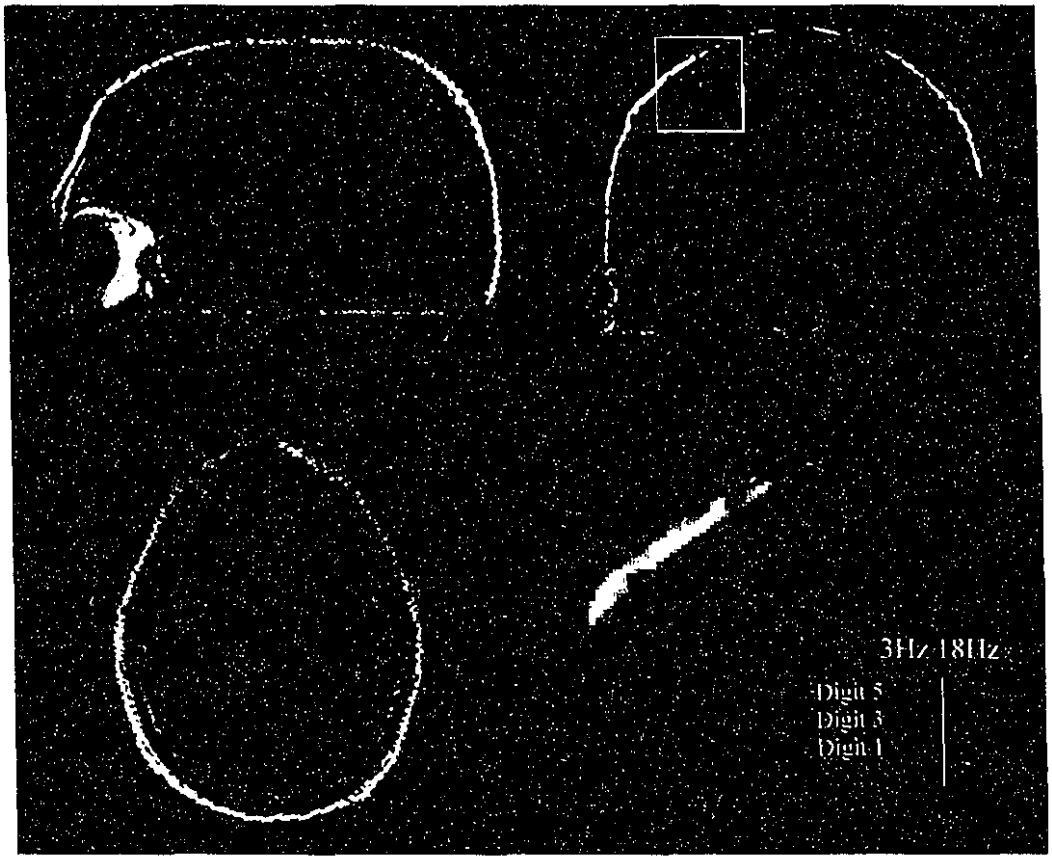


Fig. 4. Dipole positions for the five sessions for Subject 2 were averaged and superimposed on the subject's MRI. Both transient and steady-state somatotopic maps were located near contralateral area 3b, however, the solutions are anterior to know anatomical landmarks of the hand area. Digit 1 representations were observed lateral and inferior to digit 5 for both 3.1 Hz and 18 Hz steady-state stimulation.

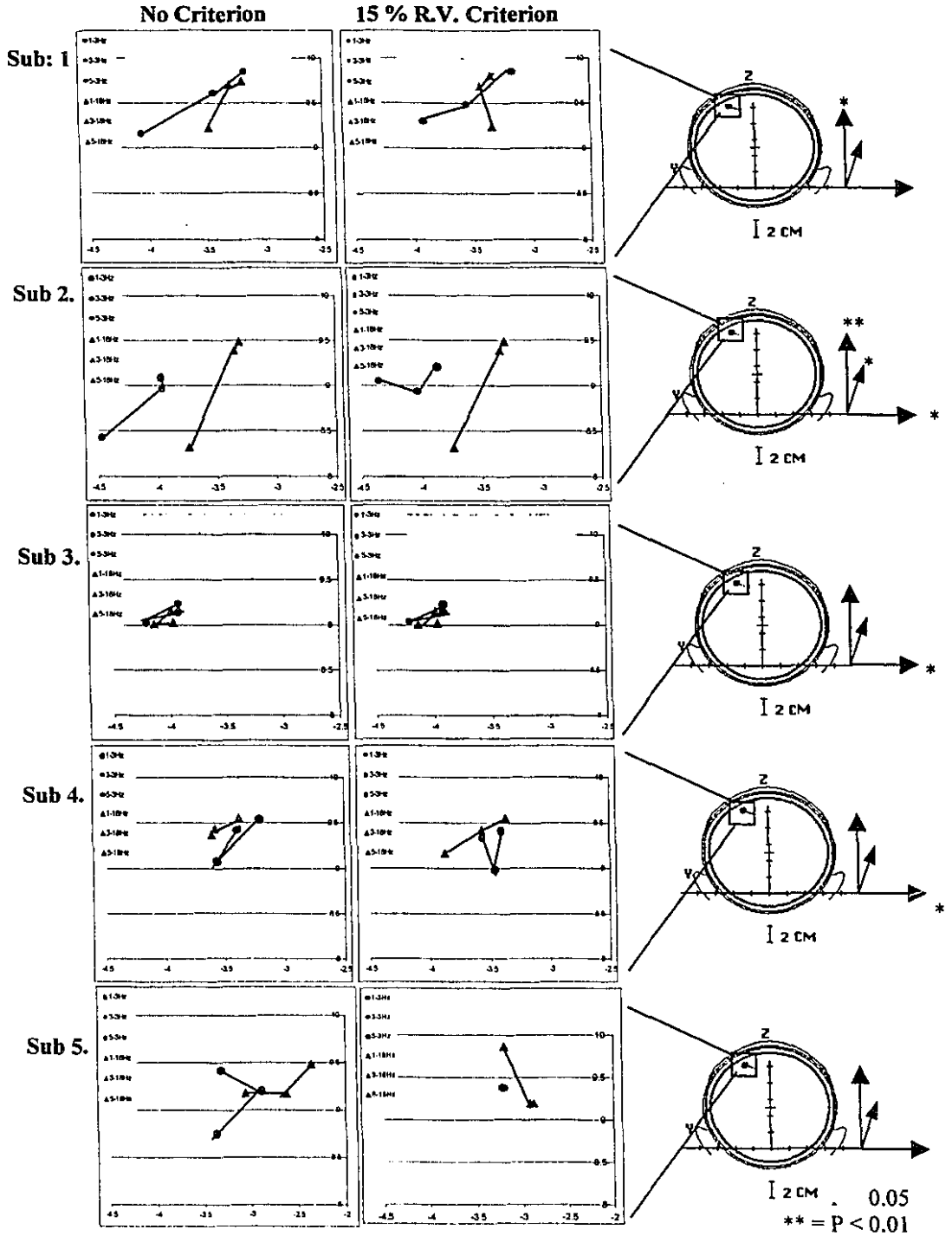


Fig 5. Somatotopic dipole maps are compared including all positions (no criterion) and with a criterion imposed on the observed solutions. Statistics were performed on dipole positions from all 5 sessions (no criterion) for X, the medial lateral coordinate, Y the anterior posterior coordinate, and Z the superior inferior coordinate. Penfield-like somatotopy, where digit 1 was observed to be inferior and lateral to digit 5 was observed for 3 out of 5 subjects using 3.1 Hz stimulation and 4 out of 5 subjects using 18 Hz stimulation (no criterion).

Table 1. Dipole Positions Collapsed Over Days

Subject	Coordinate		Effect	F	p-level
1	X	Digit	2, 8	3.812	0.069
		Freq	1, 4	0.499	0.519
	Y	Digit	2, 8	2.967	0.109
		Freq	1, 4	1.274	0.322
	Z	Digit	2, 8	8.442	0.011
		Freq	1, 4	0.012	0.917
2	X	Digit	2, 8	4.503	0.049
		Freq	1, 4	0.924	0.391
	Y	Digit	2, 8	5.445	0.032
		Freq	1, 4	7.201	0.055
	Z	Digit	2, 8	47.116	0.000
		Freq	1, 4	2.325	0.202
3	X	Digit	2, 8	5.670	0.029
		Freq	1, 4	2.897	0.164
	Y	Digit	2, 8	3.052	0.103
		Freq	1, 4	0.014	0.913
	Z	Digit	2, 8	1.771	0.231
		Freq	1, 4	0.367	0.577
4	X	Digit	2, 8	0.422	0.670
		Freq	1, 4	1.421	0.299
	Y	Digit	2, 8	1.336	0.316
		Freq	1, 4	2.077	0.223
	Z	Digit	2, 8	2.711	0.126
		Freq	1, 4	0.594	0.484
5	X	Digit	2, 8	12.756	0.003
		Freq	1, 4	85.445	0.001
	Y	Digit	2, 8	2.287	0.164
		Freq	1, 4	22.402	0.009
	Z	Digit	2, 8	2.500	0.143
		Freq	1, 4	0.513	0.513

Table 1. An analysis of variance was performed on dipole position for each subject collapsed over days. The main effect comparing dipole position among the stimulated digits (*Digit)* was observed to be significant in 4 out of 5 subjects in either the medial lateral coordinate (X) or the inferior superior coordinate (Z). The main effect comparing differences in dipole position by stimulus frequency (*Freq*) was significant only in 1 subject (subject 5) who also showed the highest residual variance (see Table 2).

Table 2. Percent Residual Variance

	3.1 Hz			18 Hz		
Subject	**Digit 1**	**Digit 3**	**Digit 5**	**Digit 1**	**Digit 3**	**Digit 5**
1	9.72	11.24	10.64	12.70	15.12	11.90
2	12.19	12.24	13.84	8.69	12.06	12.42
3	8.20	6.90	9.45	6.50	6.39	5.61
4	15.08	11.85	8.47	9.60	5.19	4.62
5	15.51	21.44	25.69	11.43	13.50	16.23
Avg	12.14	12.73	13.62	9.78	10.45	10.15

Table 2. Mean residual variance (%) for all subjects and digits shows marginally higher values for 3.1 Hz stimulation (non significant). Subject 5 showed higher than average residual variance for each digit and stimulus frequency.

Table 3. Mean Dipole Position S.D. (cm)

	3.1 Hz			18 Hz		
Subject	Digit 1	Digit 3	Digit 5	Digit 1	Digit 3	Digit 5
1	0.42	0.73	0.44	0.63	0.87	0.45
2	0.68	0.39	0.36	0.57	0.62	0.75
3	0.66	0.60	0.88	0.89	0.90	0.89
4	0.78	0.63	0.38	0.52	0.39	0.45
5	0.53	0.87	0.69	0.72	0.76	0.65
Average	0.62	0.64	0.55	0.66	0.71	0.64

Table 3. The standard deviation values for each dipole position coordinate (x, y and z) were calculated and averaged for each digit. The standard deviation for dipole positions calculated following 3 Hz stimulation ranged from 0.55 cm to 0.62 cm and 0.64 cm to 0.71 cms for 18 Hz stimulation (n.s.).

Table 4. Mean Dipole Moment nA(m)

	3.1 Hz			18 Hz		
Subject	Digit 1	Digit 3	Digit 5	Digit 1	Digit 3	Digit 5
1	3.57	4.33	4.02	1.20	1.32	1.37
2	3.21	1.66	3.33	1.34	1.03	1.23
3	6.03	5.29	4.33	1.55	1.77	1.57
4	3.03	2.83	4.59	1.39	1.68	2.09
5	4.66	3.95	3.56	1.52	2.05	2.02
Average	4.10	3.61	3.97	1.40	1.57	1.66

Table 4. Dipole moment from responses to 3.1 Hz stimulation was observed to be approximately twice as large as responses to 18 Hz stimulation, for each subject and digit. This difference was also observed for peak to peak mean amplitude values of 1.58 mV (3.1 Hz) and 0.59 mV (18 Hz).

Chapter 5

Evidence for Fusion and Segregation Induced by a 21 Hz Multiple Digit Stimulation in Humans

Preview

One mechanism by which the brain encodes dynamic somatosensory information is by means of somatopic maps. Experiment 1 (Chapter 3) showed that we can measure somatotopy with EEG using transient mechanical stimulation . Experiment 2 (Chapter 4) showed that somatatopic maps determined from steady state responses are in qualitative agreement with the observed transient maps. This experiment also demonstrated that steady state stimulation procedure is more efficient method for somatotopic mapping, as the steady state maps were determined in half the recording time with similar precision.

Experiment 3 addressed the question of whether somatotopic representations in the adult human brain are static or fixed. Are they invariant, or do they change to represent the subject's experience with somatosensory stimulation? We addressed this question by measuring steady state responses before during and after training subjects to detect changes in the frequency of 21Hz tactile stimulation applied to the digits.

I was assisted in this experiment by Dr. L. Liu who worked with me to implement the experimental procedures and collected the EEG data under my supervision. We contributed equally to the publication. The publication appeared in Neuroreport 11(10) pp.2313-2318 (2000).

COGNITIVE NEUROSCIENCE NEUROREPORT

Evidence for fusion and segregation induced by 21 Hz multiple-digit stimulation in humans

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Subjects were trained to detect changes in the frequency of 21 Hz tactile stimulation applied to digits 2+3+4 (fusion group) or 2+4 (segregation group) of the right hand. The 21 Hz steady-state response for digit 3 was measured by 64 channel EEG on mapping trials before and after training. Discrimination improved over 3 days, confirming that subjects attended to the training stimuli. The 21 Hz response was larger on training than on mapping trials, indicating sensitivity of the response to the strength of cortical activation. Under these conditions the 21 Hz response for digit 3 decreased after training in both groups on day 1. On day 3 this effect reversed in a subset of fusion subjects while segregation continued to yield decreases. The findings suggest that somatosensory representations are dynamically modified by the sensory input experienced on a task. NeuroReport 11:2313–2318 © 2000 Lippincott Williams & Wilkins.

Key words: Electroencephalography (EEG); Hebbian learning; Somatosensory cortex; Steady-state responses; Use-dependent plasticity

INTRODUCTION

Recent animal studies have shown that the receptive fields (RFs) of neurons in somatosensory cortex can be altered in adult organisms by behavioural training. For example, Recanzone *et al.* [1,2] found that training owl monkeys on a tactile frequency discrimination task enlarged the neural representation for the trained skin site by a factor of 1.5–3 in cortical area 3b. An enhancement of similar magnitude was observed by Jenkins *et al.* [3] when monkeys were trained for 50–100 sessions to touch a rotating disk with the correct pressure in order to earn food reward. Remodelling of sensory representations by behavioural procedures appears to be gated by neuromodulatory systems in the thalamus and basal forebrain that condition rapidly to cues signalling task relevant events. Remodelling does not occur unless the animal is required to process the task stimuli by discriminative training (see [4] for review).

Fusion and segregation of somatosensory representations for different skin sites has also been demonstrated by animal studies. Wang *et al.* [5] applied a series of brief, phase-coherent tactile stimuli alternatively to the distal or proximal phalanges of digits 2+3+4 of owl monkeys. The task of the monkey was to detect when pulses were delivered twice in succession to either phalange. Invasive mapping of area 3b carried out after 4–6 weeks of training revealed a high proportion of neurons (44–56%) with multiple-digit RFs that were rarely seen in untrained animals. At the same time, a band representing dorsal skin emerged between the zones representing the non-simultaneously excited distal and proximal skin surfaces, suggesting a concurrent segregation effect. Experiments on rat barrel fields indicate that lengthy training may not be necessary for the occurrence of fusion effects. Whisker-pairing leads within 24 h to fused representations which appear initially in the superficial (II, III) and deep (V, VI) layers of the barrel cortex and 10–30 days later in the input layer (IV), signifying reorganization at the level of the thalamus [6].

Wang *et al.*'s report that multiple-digit RFs were induced in ~50% of sampled neurons suggests that fusion and segregation may be detected in electrical (EEG) or magnetic (MEG) fields which can be recorded non-invasively in human subjects. In the present study we used EEG to study short-term plasticity induced by training for tactile frequency discrimination in humans. Subjects were trained to discriminate small changes in the frequency of a 21 Hz standard stimulus applied for 1 s simultaneously to the finger tips of digits 2+3+4 (fusion condition) or digits 2+4 (segregation condition) of the right hand. Based on previous animal research we hypothesised that synapses conveying input from the fingertips receiving multiple digit stimulation would be strengthened by simultaneous depolarisation of their postsynaptic targets, through a process of Hebbian learning. If so, stimulating digit 3 after training for fusion was expected to elicit a response from neurons tuned previously to digits 2 and 4, thereby augmenting the 21 Hz response. In contrast, segregation training was expected to decrease the response for digit 3 (segregated from 2 and 4) through anti-Hebbian mechanisms. Subjects were trained for 3 days to allow for the development of remodelling effects.

MATERIALS AND METHODS

Subjects: Thirteen healthy right-handed male subjects (age 24–40 years) were paid for their participation. Seven subjects were trained in the fusion condition and six in the segregation condition. Informed consent was obtained in accordance with the Declaration of Helsinki.

Procedure: Mechanical stimulation of the fingertips was generated by a five-digit stimulator constructed of solenoids connected to tactile probes (rods of 2 mm diameter). The solenoids were housed in a sound-attenuating and electrically shielded case to reduce acoustic and electromagnetic artefact. Subjects wore headphones through which low-level white noise was presented to mask residual acoustic artefact. Tactile stimulation was presented at 21 Hz (the standard frequency) or one of eight higher frequencies up to 26 Hz (the comparison frequencies). This frequency range provided the sensation of flutter and is within the resonant frequency region for the somatosensory system [7]. Stimuli were of 1 s duration and were separated by an interstimulus interval of 1 s. To ensure that somatosensory stimulation was confined to the fingertips, the subject's forearm was positioned on a platform isolated from the stimulator. Circular foam cups were placed around the perimeter of the probe tips to achieve a stable and stereotyped finger position and to maintain stimulation to the same skin area between measurements.

The experiment was carried out on 3 consecutive days. The EEG was measured on the first and last day, but not on day 2 which consisted of behavioural training only (this day was omitted for one subject). At the outset of day 1, psychophysical calibration of the 21 Hz stimulus was performed for each subject on digits 2, 3, 4 and 5, in order to achieve a detectable light flutter sensation of comparable intensity across all digits. The level of stimulation for each digit was then fixed at this intensity level throughout the experiment, individually for each subject. After stimulus calibration, the following procedures were administered in the order stated below. These procedures were repeated on day 3.

1. *Noise measurement 1 (15 min)*: In order to evaluate the artefact generated by the stimulator alone, the EEG was recorded while the stimulator was operated at 21 Hz (1 s duration) but the subject's fingers were not placed on the probes. The noise estimate consisted of all combinations of stimuli used in the experiment (specifically, digits 3 and 5 alone, digits 2+3+4, or digits 2+4). A total of 105 trials was presented for each digit condition, with the digit conditions sequentially intermixed in a random order.

2. *Mapping (30 min)*: In the mapping phase, 21 Hz stimulation (1 s) was applied separately to digits 3 and 5 for 210 trials each, in an intermixed order. Trials were grouped into three blocks consisting of 140 trials (420 trials overall) with a rest in between to allow for subject queries and eye blinks. Digit 3 was designated as the test digit because digits 2 and 4 during the fusion or segregation training spanned it. Fusion and segregation effects were predicted for this digit. We also recorded digit 5 as a control digit for the stability of mapping measurements. However, because lateral connections in area 3b could in principle extend to digit representations distal to the stimulated site, digit 5 may not be comparable to an unstimulated control condition. Data from digit 5 were excluded from the analysis.

3. *Training (60 min)*: Subjects were trained to make a same or different judgement between a standard stimulus (S1) and a comparison stimulus (S2) presented to digits 2+3+4 (fusion) or 2+4 (segregation). S1 was always 21 Hz, while S2 was either 21 Hz (50% of training trials) or varied from 22 to 26 Hz in steps of 0.5 Hz. S1 and S2 were 1 s duration and were separated by an interval of 1 s. Subjects indicated their discriminative choice after each S1/S2 trial by pressing an appropriate button using the left hand. Response latency was recorded. Feedback was given after each trial by illuminating a green (correct) or red (incorrect) LED placed in 1 m in front of the subject at eye level. The next trial commenced 1 s after the button press. There were three training blocks and 192 trials in each block. At the end of each block, subjects were told the ratio of the correct to incorrect responses to help them assess their progress. In order to ensure that S2 was discriminated for its frequency and not its perceived intensity, the duration of the square wave pulse applied to the probe solenoids (10 ms) was reduced by 0.1 ms for every frequency increase of 0.5 Hz. This adjustment was found in a separate psychophysical study to yield equal intensity functions for S2 stimuli ranging between 21 and 26 Hz.

4. *Mapping 2 (30 min)*: Mapping 2 was performed upon the conclusion of discrimination training. The procedure was identical to Mapping 1.

5. *Noise measurement 2 (15 min)*: Noise measurement 2 was identical to the first noise measurement. The two noise measurements were collapsed to give the same number of trials (210) per digit condition as was used during the mapping sessions.

The fusion and segregation conditions of this study were designed to produce opposite learned changes in the cortical representation of digit 3. Comparison of the two conditions therefore provided an assessment of whether cortical remodelling by Hebbian mechanisms had occurred. However, an unavoidable feature of the fusion and segregation manipulation is that digit 3 is stimulated during training for fusion but not during training for segregation. Hence, in principle, differences between the fusion and segregation conditions could be attributed to adaptation of the 21 Hz steady-state response by repeated stimulation of the test digit as well as to remodelling of the cortical representation for this digit. Because the expected direction of adaptation and remodelling effects was opposite, a choice between the competing interpretations was possible. We trained subjects for three days in order to allow changes consequent on Hebbian remodelling to be expressed.

EEG recording and analysis: A 64-channel EEG system (NeuroScan Inc) was used to measure brain responses to tactile stimulation. The electrode cap (Neuromedical Quik-Cap) covered the whole head with a symmetrical array that included the international 10-20 system. The EEG was recorded continuously DC to 100 Hz and sampled at 500 Hz. Electrodes Cz and AFz were selected respectively as the reference and the ground. During the recording,

subjects were instructed to keep their eyes open and blink as little as possible.

The recorded EEG was first cut into 2 s segments from 500 ms before to 1500 ms after stimulus onset and baseline corrected for each channel. Epochs contaminated by eye blinks and movement artefact (changes >100 μv at any electrode) were rejected from further analysis. EEG data for one subject in the fusion group and two in the segregation group could not be analysed owing to artefacts generated by defective lead/electrode junctions (the faulty electrode cap was subsequently replaced by Neuromedical with a modified version). Epochs for the remaining 10 subjects were averaged separately for each digit condition (3, 2+3+4 or 2+4) in each mapping and training session (for training, S1 only) and re-referenced to a common average reference.

Signal analysis was carried out in the frequency domain. Spectral power at 21 Hz was determined using Welch's periodogram method [8]. In addition, spectrograms were calculated depicting spectral power from 15 to 70 Hz over the EEG epoch (−500 to 1500 ms) for each electrode. The effect of training for fusion and segregation was evaluated by subtracting 21 Hz spectral responses recorded for digit 3 on the first mapping session (before) from the same measure determined in the second mapping session (after), for days 1 and 3 separately. Pre-planned *t*-tests were applied to these measurements in the fusion and segregation groups. In addition, before/after changes in the 21 Hz response were evaluated on days 1 and 3 by Monte Carlo simulations which modelled the distribution of map2−map1 differences under the null hypothesis separately for each subject [9]. The area above the before/after difference obtained for each subject was calculated to determine whether statistically significant changes had occurred on days 1 or 3 of discrimination training for that subject.

RESULTS

Behavioural results: The probability of a hit (P(H)) was calculated as the proportion of trials on which the subjects responded 'different' when S1 and S2 were of different frequencies (comparison frequencies of 22–26 Hz, corresponding to a Δf of 1–5 Hz). The probability of a false alarm (P(FA)) was calculated as the proportion of trials on which the subjects responded 'different' when the frequency of S2 was the same as S1 (21 Hz, Δf = 0). From these two measures a performance score P was calculated for each comparison frequency >21 Hz according to the formula $P = P(H) \times [1 - P(FA)]$, following Recanzone *et al.* [1] Psychophysical functions were constructed for each subject and training session by plotting P against all comparison frequencies >21 Hz (Δf > 0). These functions are averaged and shown in the upper panel of Fig. 1 for the fusion and segregation groups, separately. Discrimination improved over the three days in each group, particularly at frequencies adjacent to the discrimination threshold (P = 0.5, Δf ~ 2 Hz). Response latency (shown in the lower panel of Fig. 1) also decreased over successive days in the two conditions. Overall, differences in discrimination performance between fusion and segregation were not pronounced. When the number of correct responses was contrasted between days on an individual basis, 12 of 13 subjects showed improvement on last day compared to the first day of training for fusion or segregation ($p = 0.002$, sign test).

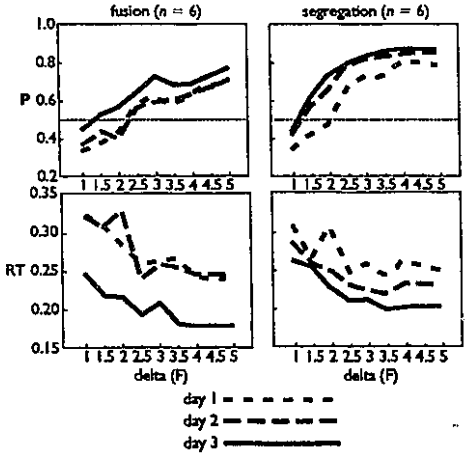

Fig. 1. Psychophysical functions over 3 days for subjects receiving 3 days of training ($n = 12$). Values of P and response time (RT, in s) are shown at the top and bottom panels, respectively, averaged separately for the fusion and segregation conditions. The lines in the top panels indicate the threshold of discrimination (P = 0.5).

EEG results: Figure 2 presents EEG data from a typical subject for digit 3 in a mapping session. Panel A shows the unfiltered data where oscillatory activity appears stronger at electrodes in the left hemisphere, contralateral to the site of stimulation. Spectral plots (15–65 Hz; Fig. 2b) confirmed 21 Hz activity in a cluster of electrodes over the left scalp. Although not apparent here, harmonics at 42 and 63 Hz were also noted in some subjects, but with lower amplitude than at 21 Hz. Spectral density is summed over all electrodes in Fig. 2c), where it can be seen that the 21 Hz response reached its peak amplitude about 300 ms after the stimulus onset. In Fig. 2d the time-domain average is given for all electrodes, bandpass filtered between 18 and 24 Hz. The scalp topography at the time point indicated in the time domain enlargement of Fig. 2e is shown in Fig. 2f, where a polarity reversal is seen over the left Rolandic fissure, consistent with a source of activation in primary somatosensory cortex. We also contrasted, for all subjects for whom EEG data were available ($n = 10$), 21 Hz spectral power during mapping measurements for digit 3 with noise measurements taken when the stimulator was operating but the finger was not in contact with the tactile probe. On average, the peak of the 21 Hz response was found to be about eight times stronger during mapping runs than during noise runs for the fusion and segregation conditions combined.

In order to evaluate whether the 21 Hz response was sensitive to the strength of cortical activation, we investigated whether the response varied as a function of the

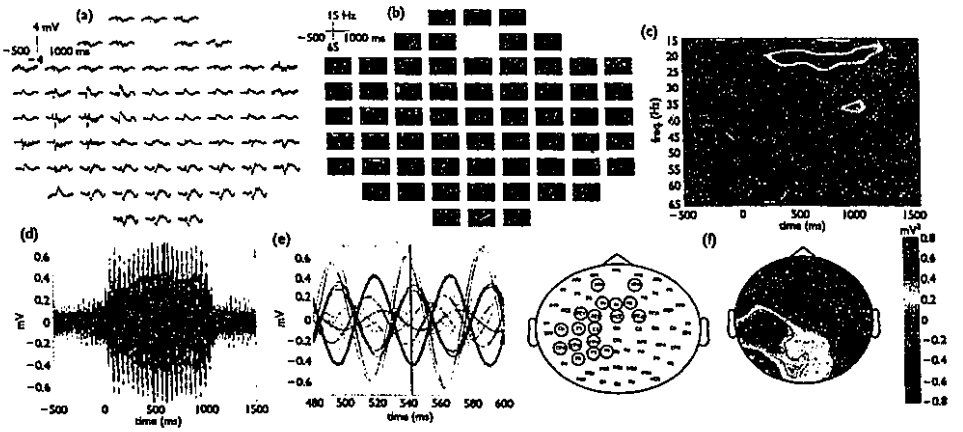

Fig. 2. EEG data from a typical subject for digit 3 in a mapping session. (a) Unfiltered EEG (−500 to 1500 ms) over 64 electrodes. (b) Spectral plots (15–65 Hz). (c) Sum of spectral density over all electrodes in (b). (d) 64-channel EEG time domain responses, filtered 18–24 Hz. (e) Time scale expanded between 480 and 600 ms in (d). (f) Right: scalp topography at 542 ms in (e); left: 64-electrode array, with 18 electrodes highlighted that gave a strong 21 Hz response.

number of digits simultaneously stimulated. For this purpose we compared the response on training trials with the response on mapping trials, separately for the fusion and segregation conditions. The results are shown in Fig. 3a (grand average for fusion subjects) and Fig. 3b (segregation subjects, days 1 and 3 shown separately). Response topography (21 Hz spectral power) on training trials is depicted on the left in each panel. In the right panel, response topography on mapping trials (digit 3 stimulated) has been subtracted from the training topography (digits 2+3+4 in fusion, 2+4 in segregation), to show the normalized difference between them. Subtraction revealed a prominent region of increased power over the contralateral Rolandic fissure for fusion and segregation, indicating stronger activation on training trials than on mapping trials in each group. This effect was quantified using a fixed montage of 18 electrodes anterior and posterior to the left Rolandic fissure (constant for all subjects; see Fig. 2f, left). Multiple digit stimulation increased the 21 Hz response by a factor of 2.18 in the fusion group compared to a factor of 1.45 in the segregation group. The difference between the groups was consistent with a near-linear increase of the 21 Hz response as a function of the number of digits stimulated on fusion and segregation training trials. This increase represents a brain response and not stimulator artefact, because noise measurements shown in Fig. 3c did not differ between 2+3+4 and 3 conditions when the digits were removed from the tactile probes. When the fusion and segregation groups were collapsed, training activations were observed to be stronger than mapping activations in every subject ($n=10$, $p=0.001$, sign test). Inspection of the right panels in Fig. 3a,b shows further that the peak of spectral power on training trials tended to be larger on day 3 than on day 1 in both conditions. When power on training trials was contrasted directly between Day 1 and Day 3 for the 18 electrode montage, a 24% increase was observed in the fusion group and 6% in the segregation group, but these increments did not reach significance.

Fusion and segregation effects were evaluated by calculating the difference in spectral power at 21 Hz between the two mappings of digit 3 (map 2−map 1, days 1 and 3 separately). These differences were determined for the 18-electrode montage of Fig. 2f and are averaged separately for the fusion and segregation groups in Fig. 4a. Inspection of the fusion group shows that the 21 Hz response for digit 3 decreased after fusion training on day 1, but increased after fusion training on day 3. The increase on day 3 and the reversal between the days were in the direction of a fusion hypothesis, but did not reach significance at the group level. Inspection of the segregation group shows that the digit 3 response decreased after training on both days. This effect was significant for the segregation group on day 3 and when the two days were averaged ($p=0.026$ and $p=0.04$ respectively, one-tailed tests). Comparison of the fusion and segregation groups overall (days 1 and 3 averaged) yielded $t(8)=1.65$, $p<0.10$ (one-tailed test). The performance of individual subjects is shown in Fig. 4b,c for fusion and segregation, respectively. Performance over days was more consistent in the segregation condition, where all subjects showed decreases in the digit 3 response in each measurement. In three of these cases (indicated by an asterisk) the decreases were statistically significant when assessed by Monte Carlo simulations. In the fusion group significant increases were detected in the 21 Hz response for digit 3 following training on day 3 in two subjects, and a significant reversal between days for one of these cases. However, one fusion subject showed a significant decrease in the 21 Hz response after training on day 3.

DISCUSSION

Several conditions were met for a test of fusion and segregation induced by cooperative 21 Hz stimulation of

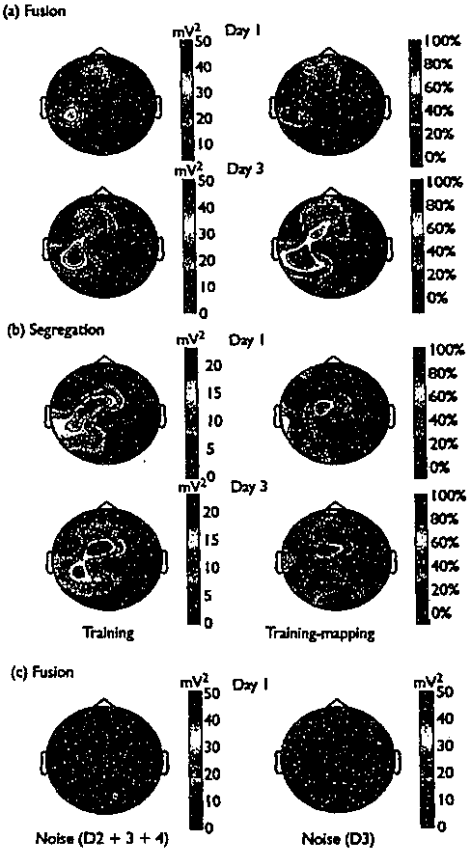

Fig. 3. Comparison of the 21 Hz response between mapping and training trials for the fusion (a) and segregation (b) groups on day 1 (top row) and day 3 (bottom row). The left column shows the topography of the averaged 21 Hz response on training trials, while the right column is the normalized difference (percentage of peak activation) obtained when the mean of the mapping trials was subtracted from the training trials. Scaling is identical for days 1 and 3 but differs between the fusion and segregation groups. (c) Noise measurements presented for the 2+3+4 condition and the 3 condition, scaled identically to the fusion group in (a, left).

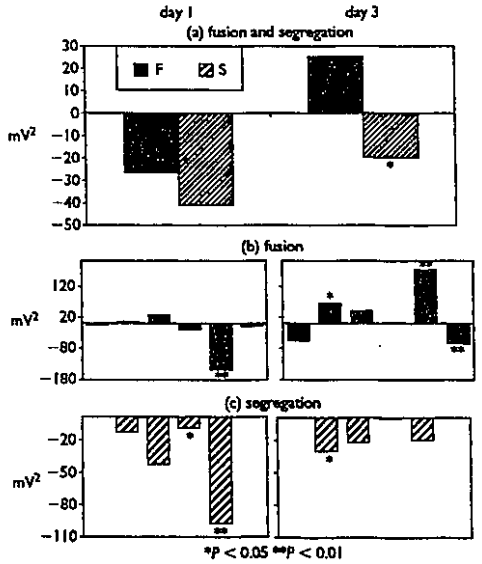

Fig. 4. (a) Change in the 21 Hz response between mapping blocks (map2–map1) separately for the fusion and segregation groups on days 1 and 3. Grand averages are shown. (b,c) Performance of individual subjects in the fusion (b) and segregation (c) conditions. Asterisks denote changes that are significant at the group level (a) and in individual subjects assessed by Monte Carlo simulation (b,c).

the digits. First, 12 of 13 subjects improved at the tactile frequency discrimination task over the 3 days of training. Clearly, subjects worked at the task and attended to the training stimuli. Second, the amplitude of the 21 Hz response at electrodes spanning the contralateral Rolandic fissure was found to be larger on training trials on which multiple digits were stimulated, than on mapping trials where only digit 3 was stimulated. This effect was proportionately larger on fusion training trials where three digits were stimulated compared to two digits during segregation. These findings establish that the 21 Hz steady-state response was sensitive to the strength of the somatosensory cortical activation, and that the multiple digit stimuli were reliably delivered to the fingers during training for fusion and segregation.

Under these conditions we observed a decrease in the mean response for digit 3 in both groups after the first day of training. Neural adaptation consequent upon repeated stimulation of digit 3 on training trials may have been responsible for decrements observed in the fusion group, since a hypothesis of cortical remodelling predicted the opposite effect. However, adaptation appears unlikely to account for the decrement seen in the segregation group, because digit 3 was not stimulated during training for segregation. On day 3, mean changes in the response for digit 3 were in accord with a fusion/segregation hypothesis in both groups. On this day statistical evidence for fusion was found for a subset of fusion subjects, although the reversal between days 1 and 3 did not reach significance for the fusion group as a whole. The performance of the segregation subjects was more consistent than that of the fusion subjects. All segregation subjects showed a decreased response for digit 3 following segregation training, and this effect reached significance at the group level on day 3 and when both days were combined. According to a segregation hypothesis, these changes occurred because phase coherent stimulation of digits 2 and 4 during

training for segregation was sufficient to depolarise area 3b neurons tuned to the intermediate digit 3, while synapses mediating input from this digit were silent. Under these circumstances digit 3 neurons switched their tuning to digits 2 and 4 by an anti-Hebbian mechanism. It may be noteworthy that the cortical response to the training stimulation increased (albeit nonsignificantly) on day 3 compared to day 1, particularly in the fusion group, as would be expected if multiple-digit receptive fields were established by cooperative stimulation on training trials.

The present results obtained non-invasively in humans are consistent with an earlier report of fusion and segregation obtained by Wang *et al.* in an animal study [5]. However, Spengler *et al.* reported different results for human subjects [10]. These investigators trained subjects on the task of Wang *et al.* for 3–4 weeks, before and after which single digit representations were imaged neuromagnetically (MEG) using an air-driven tactile probe. Representations for the trained digits measured as dipole moment decreased after training, although an increase was predicted. There are several procedural differences between the present study and that of Spengler *et al.* that may account for the different findings. We trained subjects with a high frequency flutter stimulus (21 Hz) which was within the resonant frequency of the human somatosensory system [7]. This stimulus was used for mapping as well as for training trials. In the Spengler *et al.* study the mapping and training stimuli were of lower frequency (~3 Hz) and differed between training and mapping in order to accommodate the requirements of MEG measurement. We also examined changes over a brief time period (three daily sessions, *vs*~10–20 sessions by Spengler *et al.*) and contrasted a fusion group with a segregation group for evidence of remodelling. Additional research will be required to corroborate present findings and resolve the different outcomes obtained by these two studies of fusion and segregation in humans.

Behavioural studies employing EEG and MEG measurement appear to provide useful information on how the brain supports the development of tactile frequency discrimination. Mechanical vibrations applied to the skin in the range 5–50 Hz produce the sensation of flutter [11] and activate neurons in area 3b of the primary somatosensory cortex (SI) which map somatotopically to the site of stimulation [12]. Our spectral EEG topographies are consistent with neural activation of area 3b, and spectral responses arising from this region appeared to change during 3 days of training for digit fusion and segregation. However, behavioural data reported by Spengler *et al.* [10] indicate that tactile discrimination transfers robustly to the untrained hand in human subjects. Because callosal projections from SI to the somatosensory cortices of the opposite hemisphere appear to be restricted largely to representations of the medial body surfaces and not the hand area [13–15], behavioural transfer points to the additional participation of higher levels of the somatosensory projection pathway in frequency discrimination. Callosal transfer from SII may be implicated, because there was no evidence in our EEG data for activation of ipsilateral SI during training for fusion or segregation.

CONCLUSION

Conditions for a test of fusion and segregation induced by multiple digit tactile stimulation in humans were established in the present study. Tactile frequency discrimination improved over three days of training, confirming that subjects attended to the training stimuli. In addition, the 21 Hz steady-state response increased with the number of digits stimulated on training trials, which confirmed that the multiple-digit stimuli were reliably delivered and that the 21 Hz response was sensitive to the strength of cortical activation. Under these conditions, changes in the 21 Hz response of digit 3 were obtained on the third day of training for a subset of subjects in the fusion condition and for the segregation group as a whole that were consistent with a fusion/segregation hypothesis. The findings support the view that somatosensory responses are dynamically modified to represent the pattern of sensory input experienced on behavioural tasks.

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Chapter 6

Conclusion

The basic problem addressed by the experiments of this thesis was how the human brain organizes the information transduced by the receptors of the somatosensory system, and how representations of that information are updated as a consequence of sensory experience. Two mechanisms used by the brain to encode its sensory world are somatotopic maps and plasticity. Penfield's description of somatotopic maps continues to guide our thinking about the basic organization of the somatosensory cortex; however, study of methods for describing these representations noninvasively in normal humans with high precision continues to be a rich area of research. Addressing questions about the dynamics of somatotopic maps and the conditions which allow for reorganization to occur will further our understanding of how sensory information is represented by the brain. In this chapter I briefly review the main findings of my research and address some questions raised for further study.

Somatotopic Maps

Experiment 1 of this thesis confirmed that somatotopic representations evoked by mechanical stimulation of the digits can be measured noninvasively by applying dipole analysis to EEG and MEG field patterns. This experiment was the first to provide evidence of digit somatotopy when brain responses were evoked by mechanical stimuli and measured by EEG. It is also the only experiment in the literature to compare somatotopy measured by EEG and MEG within the same subjects. Source localizations determined from both types of data projected onto a region of the postcentral gyrus as identified by anatomical landmarks observed in the subject's MRI. Overall separation from the first digit to the fifth digit on a lateral to medial plane was about 6 mm, which is broadly consistent with the observations of Buchner et al. (1995) using electrical

stimulation and with somatotopic maps measured invasively by Penfield and Boldrey (1937).

One issue to arise from Experiment 1 was that conventional stimulation protocols for somatotopic mapping which typically use transient stimulation (1-3 Hz) are not efficient. Ten minutes or more of stimulation may be required for a single digit to obtain data sufficient for source analysis. The adoption of such procedures means that temporal dynamics in somatotopic maps that are vulnerable to reset by continued stimulation cannot easily be investigated. The utility of steady-state procedures for somatotopic mapping was therefore studied in Experiment 2. We found that somatotopic maps of digits 1, 3, and 5 derived from 18 Hz stimulation were remarkably similar to those derived from 3.1 Hz stimulation. This was true in two subjects who showed substantial spread among the digits in their somatotopic maps as well as in three subjects for whom the maps were more compressed. Transient and steady state maps of both types were also stable over repeated measurements. The steady state maps were obtained, however, in half the measurement time (5 min/digit compared to 10 min/digit for transient determinations). The lower limits of steady-state mapping were not investigated. However, a possible approach warranting further study is mapping multiple digits simultaneously, when each digit is stimulated at a different steady-state frequency. Brain signals appearing at each stimulation rate reflect activation of different digits and can be separated in the frequency domain, allowing measurement of somatotopy in a single sweep of stimulation perhaps on the order of a few minutes. One such attempt has recently been reported (Diesch et al., 2001) using electrical stimulation where dipole source locations exhibited somatotopic order with overlap between neighboring digits.

Nonlinear interactions arising from multiple high frequency stimulation presented simultaneously are a possible limitation of this method. However, the similarity of our 3.1 Hz and 18 Hz steady state maps suggested that both maps tapped the same event, the P55 component of the somatosensory evoked potential observed with 3 Hz stimulation. Our choice of 18 Hz was intended to allow this to happen, and while we did not see contrary evidence pointing to possible nonlinear sources of the 18 Hz steady state response, the experiment was not a strong test for such nonlinearity.

An additional finding of Experiment 2 that warrants further discussion concerns co-registration of somatotopic maps derived from dipole analysis onto individual neuroanatomy measured by MRI. Although cortical sources projected to the region of somatosensory area 3b in the coronal section (upper right panel, Figure 3, Chapter 4), they localized about 1 cm anterior to the posterior bank of the Rolandic Fissure where their sources are known to reside based on invasive recordings. There are several possible reasons for these localization errors. The implementation of a spherical head model for EEG dipole analysis is problematic as precise information about electrode location (with respect to a real head) is lost. Alternative EEG dipole models are presently under development which use "boundary element" methods to more accurately depict the shape and borders of neuroanatomical structures in the brains of individual subjects. Boundary Element models (BEMs) not only provide a better anatomical model for dipole calculations (source space 1) but also maintain information about electrode position relative to the head (source space 2). MEG dipole analysis also involves a spherical head model. However, the magnetic fields pass through the head without distortion, and as a

result, model parameters such as radius and shells representing different tissue of the head (CSF, bone, skin, and scalp) do not significantly affect the observed solution.

A more fundamental question that should be asked is whether how adequately can we capture brain activations produced by sensory stimulation by fitting one or a few dipoles to the recorded field patterns. Our findings and those of many other investigations of somatotopy (and of maps in other sensory systems) indicate that we can localize the sources of large functional brain activations with these methods, and even investigate their dynamics. Typically, early sensory evoked potentials are studied, which produce clear dipolar electrical or magnetic field patterns on the surface of the scalp. However, stimulation of a finger tip evokes a cascade of neural events occurring in multiple regions of the somatosensory cortex (SI and SII) as well as other areas of the brain (Gelnar et al., 1998). The spatial coordinates of an equivalent current dipole fitted to a field pattern indicates the cortical center of activation but not necessarily a single brain event occurring within that region. When brain events of a longer latency are considered (>100 ms) dipolar fields may disappear altogether as activity is propagated throughout the entire brain, and single dipole fits have little justification. One area of future research involves developing new methods of signal processing that can accurately describe and localize distributed neural activity appearing in wide regions of the brain. One newly developed approach called Synthetic Aperture Magnetometry (SAM) describes changes in brain activity that occur between experimental and control conditions, as is done in tomographic maps determined from fMRI data (Cheyne et al., 2001). Unlike conventional dipole analysis, SAM analysis operates on single trial data

and requires no a priori assumptions about the number of active cortical sources or their anatomical location.

Plasticity

In Experiment 3 we used steady-state stimulation to investigate whether somatotopic representations of the fingers are statically fixed, or whether they can be remodeled by temporally coherent stimulation during a tactile discrimination task. We did not attempt dipole analysis in this experiment but instead took advantage of the fact (established in Experiment 2) that such responses appear to reflect the somatotopic organization of the fingers. Our rationale was that if temporally coherent stimulation of adjacent fingers under conditions of attention leads to the formation of multiple digit receptive fields by a Hebbian mechanism (fusion), the steady-state response evoked by stimulation of a single trained digit after training should be enhanced compared to a similar measurement taken before training. Conversely, the 21 Hz response evoked by stimulation of an intercalated untrained digit would be expected to decrease, if neurons tuned to that digit switched their tuning preference to adjoining digits by an anti-Hebbian mechanism (segregation). We found evidence for both of these effects over three days of training under fusion and segregation conditions.

It must be acknowledged, however, that while the results obtained in Experiment 3 were statistically significant at the group level in the segregation condition and for a subset of individual subjects in the fusion condition, the predicted phenomenon was not seen in every subject. In this respect the findings were not robust. Future research on this topic should seek conditions that enhance training effects, such as additional sessions of training and/or enhanced control of the stimulus-skin interface. Such studies could

also compare the effects of synchronous versus asynchronous stimulation of digits during training for fusion. Synchronous stimulation should yield a stronger effect, and asynchronous stimulation little effect, if fusion is produced by Hebbian mechanisms. The phenomena addressed in these experiments is widely believed to underlie the development of hand dystonias in musicians, typists, and other skilled occupations (Elbert et al., 1998). However, to date our published study is the only one to provide evidence for fusion and segregation of finger representations in nonclinical populations trained under laboratory conditions.

The results of Experiment 3 add to growing evidence which indicates that somatotopic representations in area 3b are not statically fixed but can be remodeled to represent the pattern of tactile stimulation experienced on a task (Buonomono & Merzenich, 1998; Wang et al, 1995). Because the changes that we observed were detected on test trials on which a single digit was stimulated while the trained stimulus pattern was removed, we have reason to suggest that neuroplastic changes at the synapse were responsible for the fusion and segregation effects that occurred. However, there is growing evidence from animal studies (Moore et al., 1999) and human investigations (Noppeney et al., 1999; Braun & Wilms et al., 2000; Braun & Schweitzwer et al., 2000) that neurons in the primary somatosensory cortex have multiple tunings that can be expressed within a fraction of a second, depending on the pattern of stimulation that is present (context) as well as upon the information processing requirements of a task when stimulus pattern is held constant (attention). We have not investigated the effects of context and attention in our studies. However, it should be noted that outside of the experimental situation our subjects undoubtedly experienced complex patterns of

synchronous and asynchronous stimulation of the digits in the course of their daily lives. To the extent that these patterns are experienced under repeating and stable task conditions, changes in somatotopic organization mediated by neuroplastic mechanisms would be expected to occur. One is led to ask how these multiple representations are represented in the brain and called out to support different task requirements. In this respect, it is plausible to suggest that cues arising from the training context are also encoded during performance, and that newly-formed somatosensory representations are modulated by this input. A process of this type may have contributed to the expression of fusion and segregation in our study where evidence of these effects was observed even though subjects almost certainly experienced additional sensory input to the trained digits in their natural environments. The uniqueness of the stimuli that we delivered (21 Hz multiple digit stimulation) is an additional determining factor which may have helped to preserve the changes that were induced in the laboratory setting.

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