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Event-Related Potential Studies of

Somatosensory Detection and Discrimination

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Abstract

This thesis contains four studies, the first examining methodology issues and four subsequent ones examining somatosensory cortical processing using event-related potentials (ERPs).

The methodology section consists of 2 experiments. The first compared the latency variability in stimulus presentation between 3 computers. The second monitored the applied force of the vibration stimuli under experimental conditions to ensure that the chosen method for somatosensory stimulus presentation was consistent and reliable.

The next study involved 3 experiments that aimed to characterize the mid to long latency somatosensory event-related potentials to different duration vibratory stimuli using both intracranial and scalp recording. The results revealed differences in the waveform morphology of the responses to and on-off responses, which had not previously been noted in the somatosensory system.

The third and fourth studies each consisted of 2 experiments. These examined the discrimination between vibratory stimuli using an odd-ball paradigm to try to obtain a possible 'mismatch ' response, similar to that reported in the auditory system. The aim of this study was to clarify some of the discrepancies in the literature surrounding the somatosensory mismatch response and to further characterize this response. The results from intracranial and scalp ERP recordings showed a two-component, negative-positive mismatch response over the anterior parietal region and a negative component over the superior pre-frontal region in response to changes in both frequency and duration. The negative component over the frontal region had never before been described.

The last study explored possible interactions between somatosensory and auditory cortical potentials in response to spatially and temporally synchronized auditory and vibratory stimuli. The results showed clear interactions in the cortical responses to combined auditory and somatosensory stimuli in both standard and mismatch conditions.

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Chapter 1: General Introduction

1.1 Introduction

> All that we need notice here is, the extent to which in the human race a perfect tactual apparatus subserves the highest processes of the intellect. I do not mean merely that the tangible attributes of things rendered completely cognisable by the complex adjustments of the human hands, and the accompanying manipulative powers have made possible those populous societies in which alone a wide intelligence can be evolved. I mean the most far reaching cognitions, and inferences the most remote from perception, have their roots in the definitely combined impression in which the human hands can receive. (H. Spencer, 1855)

The roots of cognition lie in the information received from our environment. Our initial awareness of the world is based on information arising from first order afferent input from several sensory systems. This initial input is often referred to as sensation and are the sensory processes used to detect a stimulus or some aspect of a stimulus. From this input the brain derives a constantly changing, slightly delayed representation of the external environment and this is the basis of perception. Perception is the process of interpreting sensations. It includes the recognition that stimulation has occurred and the ability to discriminate between stimulus features to produce an internal representation of the environment (Levine and Shefner, 1991). The abstract constructions about objects and events arising from these representations are determined by the selective filtering and transforming functions of the receptors, of the intrinsic operating characteristics of the neural networks involved and by the effects of learning and previous experience. The challenge is to seek understanding of the underlying neural events that lead to the conscious perception of the world and to explain these perceptions in terms of neural events.

The complexity of multisensory input has led most researchers to focus on only one or two sensory systems at a time and accordingly this thesis follows tradition and will focus primarily on the somatosensory system. The sense of touch plays a vital role in the ability to function within an environment. It not only provides basic tactile information, such as textures or edges of objects, it is also used extensively in nonverbal communication; a touch can convey anger, love, friendship, rejection or aggression depending on the behavioural context. However the neural events underlying even the most elementary of tactile mechanisms are still only poorly understood. One of these mechanisms is tactile sensory discrimination. The ability to detect a change in somatosensory input is used on a daily basis often without awareness; even walking down the street you will notice a change in tactile input if you step on a sheet of ice, but what are the neural processes underlying this mechanism? Before we address even a small part of this question we will begin with a brief overview of the neuroanatomy of the somatosensory system, of what is already known about sensory discrimination and of how sensory memory may be involved.

1.2 The Somatosensory system

The somatosensory system consists of at least three different spinal cord pathways that mediate tactile sensations, such as pain and temperature, discriminative touch and proprioception, and each of these pathways projects to a different target within the brain. Tactile sensations are complex because they involve blending a variety of sensations from these different pathways. For example touching the door of a car would involve light cutaneous contact, temperature and proprioception information from the arm and hand as well as ongoing information from other parts of the body, including lower limbs and

viscera not directly involved in the ongoing task. The anatomy of the somatosensory system covers a large number of interconnected peripheral and central nervous system pathways. Therefore, as the experiments described in this thesis use vibration stimulation applied to the fingertips and discriminative touch, this overview of the anatomy of the somatosensory system will focus mainly on the somatosensory pathways thought to mediate this information.

1.2.1 Peripheral receptors

All sensory pathways begin with peripheral receptors that transmit signals to the central nervous system conveying information about a stimulus and in the somatosensory system the skin contains the majority of these receptors. Two main types of skin in the body of humans are glaborous, found on the palm of the hand and sole of the foot, and hairy, found on most other parts of the body (fig. 1.1). The peripheral receptors activated will vary depending on the type of skin stimulated.

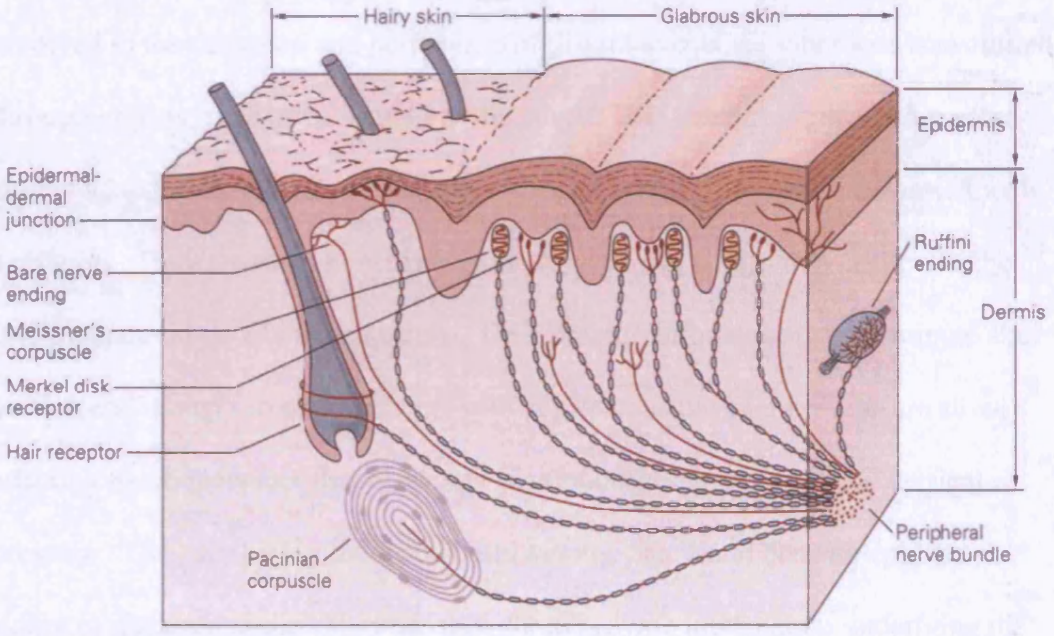


Figure 1.1: Sectional view of hairy and glaborous skin with mechanoreceptors (Kandel, et al., 2000, p. 433).

In addition to the type of skin, the stimulus information to be conveyed will also determine which peripheral receptors will be activated. In the somatosensory system there are roughly three main categories of stimulus information, discriminative touch, pain and temperature and proprioception, and the each category relies on different receptors. Discriminative touch includes touch, pressure and vibration perception. It relies mainly on four different receptor types found in glaborous skin: 1) Meissner's corpuscles. 2) Pacinian corpuscles. 3) Merkel cells. 4) Ruffini endings. (fig. 1.1) The first two are rapidly adapting receptors and the latter two are slowly adapting receptors. These receptors are referred to as mechanoreceptors as they respond to mechanical stimuli such as vibration, tension or pressure. Their characteristics are summarized in table 1.1.

Pacinian corpuscles are subcutaneous and most numerous along the sides of the fingers. The cutaneous nerves supply them directly and they can handle up to 600 stimuli per second, which renders them optimal for signalling vibration from either the overlying skin or from the underlying bone. They are thought to be involved in the detection and perception of distant events via vibrations transmitted through objects, such as tools held in the hands. Meissner's corpuscles are more slowly adapting than the Pacinian corpuscles and mediate superficial phasic touch sensation. They are most numerous in the finger pads, where they lie beside the intermediate ridges of the epidermis. They provide information about minute skin motion and thought to play a critical role in grip control. Merkel cells are slowly adapting touch receptors that discharge continuously during sustained vertical pressure. They are highly modified basal keratocytes found beneath epidermal ridges in glaborous skin. They are thought to provide information underlying the perception of form and texture. Ruffini endings are slowly adapting stretch

receptors that give a sustained response when the skin is stretched in their long axes. They are found in the deep dermis and respond when heavy objects are gripped. The information from these receptors provides information for the perception of hand conformation and for forces acting on the hand. (Johnson et al., 2000).

Receptor	**Stimulus**	**Sensation**	**Adaptation**
Merkel cells	Steady indentation	Pressure	Slow
Meissner's corpuscle	Low frequency vibration	Gentle fluttering	Rapid
Ruffini's corpuscle	Rapid indentation	Stretch	Slow
Pacinian corpuscle	Vibration	Vibration	Rapid

Table 1.1: Characteristics of the mechanoreceptors found in glaborous skin that mediate discriminative touch.

1.2.2 The somatosensory pathways from spinal cord entry to brain

1.2.2.1 The dorsal column-medial lemniscus system

This pathway is essential for discriminative tactile sensation including two-point discrimination, stereognosis and complex tactile discrimination. It is also responsible for the sense of flutter vibration. It provides information about the place, intensity and temporal and spatial patterns of neural activity evoked by mechanical stimulation of the skin. Fibres mediating proprioception and other fibres involved in aspects of touch, pressure, flutter-vibration and kinesthesis ascend through the posterior funiculi of the cord and medial lemnisci of the brain stem to the ventral posterolateral nucleus (VPL) in thalamus. Afferent fibres from the lower body (trunk and legs) form the midline fasciculus gracilis and lateral to this are the upper body (trunk and arms) afferent fibres constituting the fasciculus

cuneatus. These tracts are referred to as the dorsal column pathways and terminate in the nucleus gracilis and nucleus cuneatus respectively. Fibres from the cells in these nuclei are from the internal arcuate fibres and immediately cross to the other side in the decussation of the medial lemniscus. As the medial lemniscus they will ascend to the thalamus and synapse in the VPL. Thalamocortical afferents from the VPL travel up through the internal capsule to the primary somatosensory cortex.

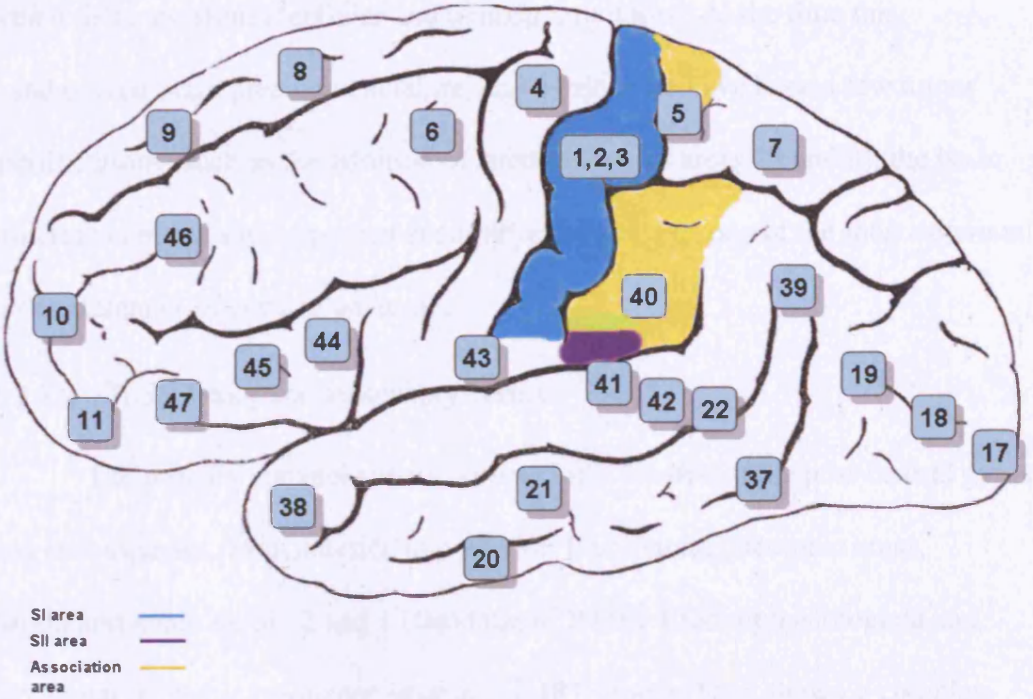
1.2.2.2 The lateral cervical system

The lateral cervical system mediates proprioception, touch and vibration. Almost all the cells are sensitive to light mechanical stimulation of the skin of the ipsilateral side of the body, though some do respond to noxious stimuli. Afferent nerve fibres entering this pathway make synaptic connections the entire length of the spinal cord. Then heavily myelinated secondary afferents ascend ipsilaterally in the most dorsal corner of the lateral funiculus to terminate in the lateral cervical nucleus, which is found lateral to the dorsal horn of the first and second cervical segments. The axons of these cells cross the spinal cord in the ventral white commissure to join the contralateral medial lemniscus to terminate in the thalamus. From there thalamocortical afferents travel to the primary somatosensory cortex (Gilman and Newman, 1992).

1.2.3 The primary and secondary somatosensory cortices

1.2.3.1 Brodmann areas

In 1909, the German anatomist, Korbinian Brodmann developed a map of the brain based on differences in cellular architecture (Brodmann, 1909).



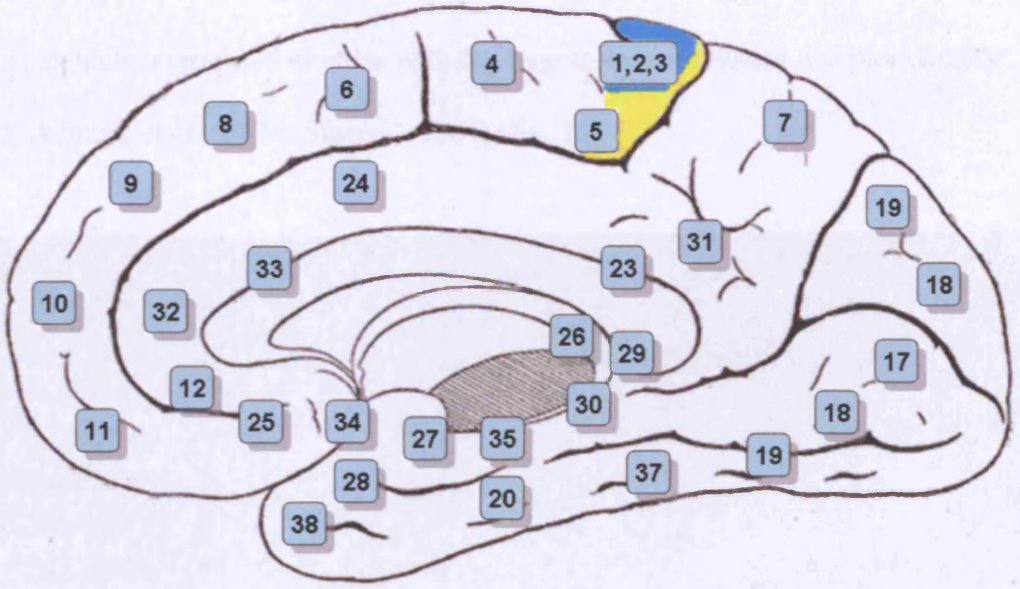


Figure 1.2: Schematic depiction of Brodmann's cortical map. The primary, and secondary somatosensory cortices and a somatosensory association area are highlighted. (Brodmann, 1909)

Brodmann areas (fig. 1.2) are the numbered subdivisions of this map in which there are similar cellular and laminar structures. At the time this standardized brain area nomenclature, and while there have been a few minor modifications (such as the addition of subdivisions of areas 23 and 3), the basic structure continues to be proven accurate and it remains one of the most commonly used references of cortical anatomy.

1.2.3.2 The primary somatosensory cortex

The primary somatosensory cortex (SI) is located in the post-central gyrus and encompasses, from anterior to posterior, four cytoarchitectonic areas, Brodmann areas 3a, 3b, 2 and 1 (Brodmann, 1909). Electrophysiological and functional magnetic resonance imaging (fMRI) studies have shown a complete body map with the largest cortical representations of peripheral sites, like fingers or lips, which correspond to areas with the largest somatosensory receptor density (Nakamura et al., 1998; Stowell, 1984) (fig. 1.3).

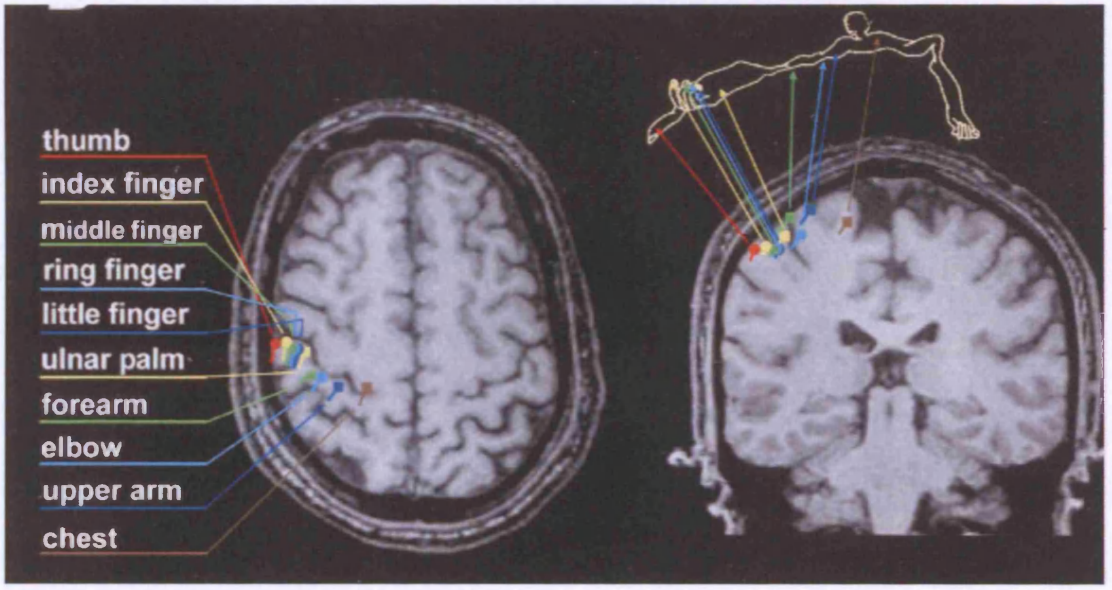


Figure 1.3: fMRI estimation of the homunculus of the primary somatosensory system (Nakamura et al., 1998).

Studies on the monkey somatosensory system show multiple representations of the body map exists in the cortex, with each Brodmann area containing a complete body map that appears to function independently of the each other (Nelson et al., 1980; Pons et al., 1985, 1987). For the most part, input to SI comes from the contralateral side of the body; however there has been some evidence of direct afferent input to the ipsilateral side (Kanno et al., 2003). Areas 3a and 3b receive the densest thalamo-cortical projections (generally from the ventral, posterior lateral nucleus) and in turn project to areas 1 and 2. Areas 1 and 2 are themselves connected anteriorly to the motor areas and to posterior association areas (Jones, 1986). In humans, lesions of SI result in broad sensory impairments including loss of two-point discrimination, localization of touch, position sense and stereognosis. Basic sensations in touch, pain and temperature are relatively preserved.

1.2.3.3 The secondary somatosensory cortex

The secondary somatosensory cortex (SII) is located on the inner part of the parietal operculum, adjacent to the dorsal insula in Brodmann area 40 (fig. 1.2) and is anatomically smaller than SI. FMRI and monkey studies have shown independent body maps in SII with enlarged hand representations similar to that observed in SI (Burton, 1986; Hari et al., 1993). However somatotopy in SII appears to be less precise with a greater degree of functional overlap (Ruben et al., 2001; Simoes et al., 2001) and single cell recordings in primates show neurons with receptive fields larger than those of the primary somatosensory cortex. Anatomic and physiological evidence confirms that SII receives input bilaterally (For review see Burton, 1986) though there remains a contralateral emphasis. The anterior region of SII is connected most strongly with SI, with inputs from Brodmann areas

3 and 1 (fig. 1.2) and it is possibly more responsive to cutaneous stimulation than the posterior areas (Burton et al., 1995). The main output projections are to the ventral parietal region and area 7. Functionally SII has been associated with processing of temporal features of somatosensory stimuli (Burton and Sinclair, 1991), with sensorimotor integration (Huttunen et al., 1996), with tactile attention (Mima et al., 1998) and with tactile learning (Ridley and Ettlinger, 1976). It may also, with other parietal regions, be involved in integrating bilateral somatosensory information (Manzoni et al., 1986; Ridley and Ettlinger, 1976).

1.2.3.4 Connections between the primary and secondary somatosensory cortices

Traditionally it has been thought a serial, hierarchical processing existed between SI and SII with direct afferent input entering the contralateral SI with connections subsequently occurring bilaterally in SII. However more recent evidence suggests parallel processing occurs at a much earlier stage (Karhu and Tesche, 1999) with functional studies in monkeys showing preserved SII responsiveness despite the inactivation of SI (Zhang et al., 2001). The anatomical connections provide evidence of a framework for this interaction. Anatomical evidence shows that the cytoarchitectonic areas of SI are connected reciprocally with the ipsilateral SII, but the main contralateral connections to SII may actually be in Brodmann area 2 (Manzoni et al., 1986). In addition, area 3b has callosal connections with the association areas in the parietal ventral area and SII is densely interconnected with this area both contralaterally and ipsilaterally (Krubitzer and Kaas, 1990). These callosal connections are organized somatotopically (Manzoni et al., 1986) and appear to duplicate the connections between SI and SII in the ipsilateral hemisphere (Karhu and Tesche, 1999).

1.2.4 Association cortical areas of the somatosensory system

Based on the traditional hierarchical theory of cortical processing, sensory information channelled through SI and SII would then be subjected to elaboration and analysis in higher association cortical regions. These regions were then divided into unimodal and heteromodal areas. The unimodal association area lies in the superior parietal lobule (Brodmann area 5 and the anterior part of 7) with projections to the heteromodal association area in the posterior part of Brodmann area 7 and the inferior parietal lobule. In addition to these traditional regions, there have been reports of direct connections to multimodal regions in the frontal lobes (Huang et al., 2005). It is generally believed several parallel processes are occurring through the same hierarchical processes. However reports of possible multimodal associations occurring at the SI/SII level suggest that the traditional view of these cortical regions may be need to be amended.

1.3 Sensory discrimination

Sensory discrimination is the ability to detect small differences between two objects or to detect a change in a stream of stimuli. It is one of the integral processes upon which perception is based and it involves a succession of events, which are dependent on the physical and contextual features of the stimuli. In order for discrimination to occur there must be cortical processes capable of comparing a new internal representation of the environment to the existing one. This ability to detect changes in the environment and modify behaviour in response to these changes is a key factor in learning and survival.

1.3.1 The cortical process of tactile sensory discrimination

1.3.1.1 Serial and hierarchical sensory processing

The prevailing model of sensory processing in the cortex, including sensory discrimination, has been that of a serial or substantially serial processor (Verleger, 1997) operating in a hierarchical manner that has been largely based on Brodmann's cytoarchitectural map (section 1.2.3.1, Fig 1.2). In this model the different modalities of sensory information emanating from a single object are analysed extensively in their respective unisensory systems before being combined in higher order multisensory areas of the cortex. In the somatosensory system, primate studies have shown an increasing complexity of receptive field characteristics from area 3b to areas 1, 2 and 5 (Iwamura et al., 1980, 1983, 1994; Sur et al., 1985). It has been assumed that this increase in complexity reflects the convergence of multiple inputs to single neurons via serial cortico-cortical connections and thus hierarchical processing (for review see Iwamura, 1998). Anatomical and physiological primate studies have also suggested hierarchical processing between SI and SII (Burton et al., 1995; Pons et al., 1992). Human studies examining the temporal relationships of cortical activations using magnetoencephalography and event-related potentials also provide support for a hierarchical and serial model of cortical processing (Bodegard et al., 2001; Inui et al., 2004).

1.3.1.2 Alternatives to serial, hierarchical models

A number of studies suggest that a serial, hierarchical model of sensory discrimination is overly simplistic. Electrophysiology and imaging studies provide evidence of multiple parallel branches existing in the stimulus processing sequence with parallel tactile processing starting at the SI and SII level (Bohlhalter et al.,

2002; Knecht et al., 1996; Zhang et al., 1996, 2001). Similarly, anatomical and magneto-electrophysiological studies have found multisensory convergence occurring in brain regions previously thought to be unisensory and interactions between the different sensory modalities occurs earlier than previously thought (see section 8.1.1). It is quite probable that both types of sensory processing exist, which would permit a more flexible discrimination processing system.

1.3.2 Maturational changes in sensory discrimination

The ability to discriminate between sensory inputs improves steadily between infancy and adolescence. Prolonged reaction times and increased error rates in children have been reported from many different paradigms in the context of attention and information processing efficiency (for review see Ridderinkhof and van der Stelt, 2000). There are several possible explanations including immature sensory processing, different task strategies from adults or reduced memory capacity. In addition, the threshold for the attention switch to a change in the environment seems to be lower in younger children than in older children or adults. This implies that the ability to ignore or inhibit processing of task-irrelevant stimuli is poorer in younger children than in older children and adults (for reviews see Gomes et al., 2000; Halperin et al., 1994; Ridderinkhof and van der Stelt, 2000).

1.4 Memory

Memory is broadly defined as the capacity of an organism to store, retain, and subsequently recall and utilize, information about itself and the environment in which it lives. There are several models of information processing and memory, most of which are based on cognitive information processing frameworks and only

superficially on the underlying neuroanatomy and neurophysiology. As a result these arguments continue to be inconclusive. Electrophysiological studies, such as those performed in this thesis, provide information regarding the underlying neural mechanisms of information process and ultimately help to refine these models.

One of the most widely accepted models is the stage theory. As a large majority of the literature uses this theory as a conceptual framework for characterizing the processes of sensory discrimination and this thesis will also utilize the basic tenets and terminology of this theory.

1.4.1 The stage theory

The stage theory is based on the work of Atkinson and Shriffin (1968) and it focuses on how information is stored in memory as opposed to how it is accessed and retrieved. This model proposed that information is processed and stored serially in three stages which are loosely based on the duration of memory retention: sensory memory (<2s), short-term/working memory (10-20s), and long-term memory (up to many years) (fig. 1.4).

1.4.1.1 Sensory memory

Sensory memory corresponds approximately to the initial moment that an item is perceived and is considered the first level of memory. Sensory memory allows us to take a 'snapshot' of our environment, and to store this information for a short period until we can attend to some of it. Each sensory modality is considered to have its own sensory memory: iconic memory for visual stimuli, echoic memory for aural stimuli and haptic memory for touch stimuli. Only information that is transferred to another level of memory will be preserved for more than one or two seconds.

The characteristics of sensory memory include: 1) A high capacity for registering data. 2) The information in the sensory memory is un-interpreted and outside of conscious control. 3) It is short, operating within the approximate time frame of 1-3 seconds.

If information in the sensory memory is to be used, it must quickly be encoded into a more durable form, i.e. short-term/working and long-term memory. Processing begins with attention, which selectively determines what will 'get through' for further examination and what will not. Attention allows parts of the stimulus to be focussed on and thereby improving the recognition of some of its features. Obviously any shortcomings in sensory memory can create problems for further processing of sensory information.

1.4.1.2 Short-term or working memory

Working memory refers to the process of maintaining representations of sensory information in conscious awareness when that information is no longer available to the senses and to its manipulation and use in guiding behaviour. Working memory is thought to contribute substantially to a number of essential cognitive functions, such as general intelligence, learning and reasoning, and language comprehension (Baddeley, 2003; Engle et al., 1999; Jonides, 1995). The most common model of working memory is that by Baddeley and Hitch (1974) which proposes the existence of a multiple component model including a central executive that controls and manipulates information held in modality-specific storage systems (buffers).

Working memory is characterized by a limited capacity for holding data and in that it requires attention for encoding. It operates within a time frame of 10-

20secs, but rehearsal strategies, such as visualization or repetition may increase this time-frame and its capacity for holding data (for review see Fuster, 1999).

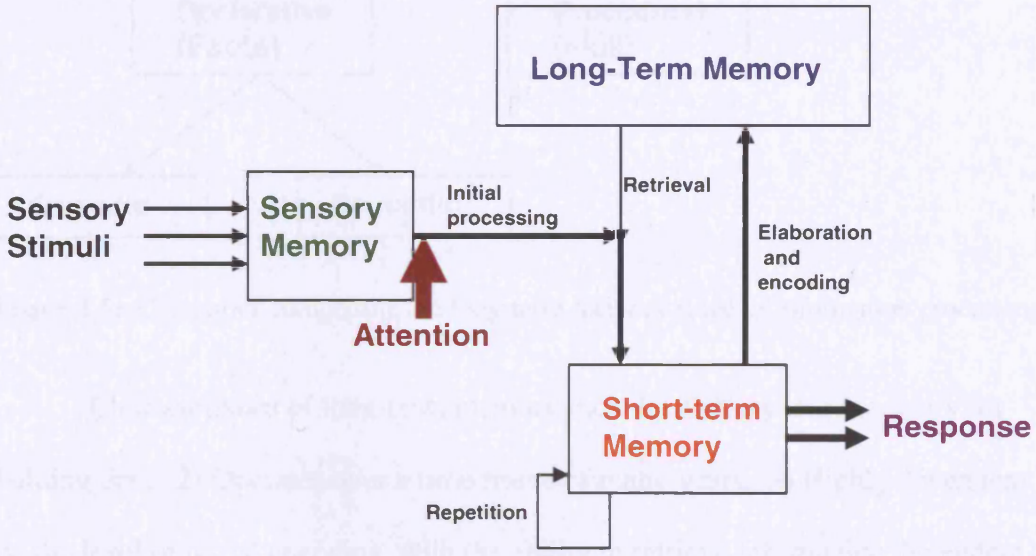


Figure. 1.4: Schematic of the Stage theory of information processing (based on Atkinson and Schriffin, 1968).

1.4.1.3 Long-term memory

Long-term memory is intended for the storage of information over a long period of time with little decay. There is thought to be two categories of long-term memory: declarative for facts and procedural for skills. Declarative memory is then subdivided into episodic and semantic memory. Episodic memory covers memories of events and experiences while semantic memory covers facts, concepts and skills. The information in semantic memory can be derived from episodic memory, such that new facts or concepts may be encoded from experience. (Guo et al., 2006) (fig. 1.5).

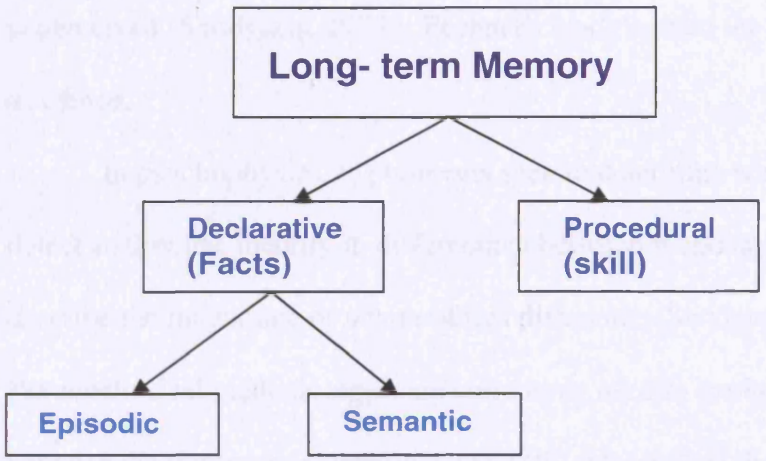


Figure 1.5: Categories comprising the long-term memory stage of information processing.

Characteristics of long-term memory include: 1) Very large capacity for holding data. 2) Operates over a time frame of many years. 3) Highly dependent on the level of initial encoding, with the ability to retrieve information dependent on how well the information had originally been acquired. 4) Data is stored in specific categories dependent on the type of information the memory contains and the behavioural operations it controls (for review see Fuster, 1999).

1.5 Techniques for studying sensory discrimination

1.5.1 Psychophysics

Psychophysics is a subdiscipline of psychology that examines the relationship between physical stimuli and their subjective correlates, or percepts. It is concerned with the processes of the sensory systems rather than the physiology. It was founded in 1860 by Gustav Theodor Fechner with the publication of Elemente der Psychophysik (Fechner, 1860). He described research relating physical stimuli with how they are perceived and set out the philosophical foundations of the field. Fechner wanted to develop a theory that could relate matter to the mind, by describing the relationship between the world and the way it

is perceived (Snodgrass, 1975). Fechner's work formed the basis of psychology as a science.

In psychophysics, experiments seek to determine whether the subject can detect a stimulus, identify it, differentiate between it and another stimulus, and describe the magnitude or nature of this difference (Snodgrass, 1975). Psychophysical methodologies are commonly used to explore the relationship between the observer's psychological states, assessed via their responses in a simple task, to finely controlled manipulations of the physical stimulus. Psychophysicists usually employ experimental stimuli that can be objectively measured, for example pure tones varying in intensity, or lights varying in luminance, and these stimuli are generally chosen carefully to specifically target the perceptual process of interest. All sensory modalities have been studied: vision, hearing, touch (including skin and enteric perception), taste, and smell. Broad areas of investigation include measurements of sensitivity, signal detection theory and sensory discrimination.

1.5.2 Haemodynamic/metabolic techniques

Haemodynamic imaging techniques make the assumption that task-induced neuronal activity is related to changes in both local cerebral blood flow and oxygen metabolism. These circulatory changes are then used to derive inferences about the underlying neuronal activity and provide indirect measures of this activity. While the spatial resolution of these techniques is good, the slow nature of the circulatory changes and the image acquisition time results in relatively poor temporal resolution. The two main methods used to study sensory discrimination are positron emission tomography (PET) and functional magnetic resonance imaging

(fMRI). These types of studies are best suited to the localization of brain areas involved in sensory discrimination.

1.5.2.1 PET

PET monitors task-related changes in regional cerebral blood flow or the corresponding blood volume via the injection into the blood stream of a radioactive solution containing positron-emitting atoms. These positrons interact with electrons to produce photons of electro-magnetic radiation whose position and trajectory can be determined and reconstructed during scanning. The images of the blood flow under different experimental conditions are compared and brain regions implicated in the performance of the task may be isolated. The spatial resolution of this technique is in the order of 4-6mm and the temporal resolution is 90-120sec (Herscovitch et al., 1983; Raichle et al., 1983).

1.5.2.2 fMRI

Oxygenated and deoxygenated bloods have different magnetic properties and these can be capitalized upon to provide a natural contrast agent, the blood oxygen level-dependent (BOLD) effect. This allows for the monitoring of blood flow changes without the use of a radioactive substance such as that used in PET scanning. In fMRI scanning, a subject is placed in a high magnetic field and task-induced changes in brain metabolism alter the ratio of oxy-and deoxy-hemoglobin locally causing measurable changes in magnetic resonance signal intensity (Kwong et al., 1993; Ogawa et al., 1992). FMRI has an optimal spatial resolution of 0.5-1mm, thus giving this technique a higher spatial resolution than PET. However the BOLD response is still relatively slow compared to electrical or magnetic methods, with a temporal resolution of around 250ms (Pfeuffer et al., 2001).

1.5.2.3 Electrical/magnetic techniques

In contrast to PET and fMRI, the electro-magnetic techniques provide a direct measure of cortical activity, either by recording the electrical fields produced by neuronal activity using the electroencephalogram (EEG) or by recording the associated magnetic fields using the magnetoencephalogram (MEG). The transmission of the neuronal currents is nearly instantaneous, providing a temporal resolution in the order of milliseconds. However the spatial resolution of these techniques is restricted by the need to calculate the signal source in three dimensions based on the two-dimensional information provided by the electrodes. This is the basis of the so-called "inverse problem" (see section 2.1.3). These types of studies are ideally suited for testing theories concerning the time course of cerebral events associated with discriminatory behaviour.

1.6 Aim of this project

The aim of this project was to examine the effects of stimulus parameters on tactile sensory discrimination and haptic memory as recorded using electrical techniques. In order to do this, event-related potentials were recorded in response to series of vibration stimuli presented using an odd-ball paradigm. The experiments described in chapter 4 address two technical issues; the synchronization of stimulus presentation with trigger output and the consistency of stimulus intensity. The characteristics of the standard somatosensory electrical response to stimuli varying in duration were explored in the experiment outlined in chapter 5. This was necessary as these stimuli were to be used in subsequent experiments. Chapters 6 and 7 describe experiments addressing the question as to the nature of the somatosensory response to a change in a stream of continuous stimuli and how the stimulus characteristics affect this response. The final

experiment is reported in chapter 8 and this study aimed to record ERP interactions between temporally and spatially concordant audio and somatosensory stimuli, with particular interest in those ERPs thought to reflect sensory discrimination processes (see mismatch processing, chapter 3).

1.7 Declaration of work done

Following discussions with my supervisors, Dr. S. Boyd and Prof. A. Towell, I designed the experiments, followed them through every stage of the process of Ethical approval (appendix 1) and recruited the subjects (for examples of the consent forms appendix 2 and subject information sheet see appendix 3). In collaboration with Alan Worley, a biomedical engineer, I designed and carried out the calibration studies described in chapter 4. With the assistance of Ralph Smith, a computer engineer, I wrote the software program that presented the various stimuli used in the experiments described in this thesis. I carried out all the data collection and, undertook the data analysis, with particular assistance in the statistical analysis from Prof. Towell. I confirm that this thesis, and the work represented in this document, is the result of my own efforts under the aegis of my supervisors.

Signature of student:

Signature of principle supervisor:

Chapter 2: Event-related Potentials – Principles and Background

2.1 Principles of event-related potentials

2.1.1 Definition

Event-related potentials – "the general class of potentials that display stable time relationships to a definable reference event" (Vaughan, 1969)

Event-related potentials (ERPs) are small changes in electrical activity of the brain elicited in response to an event. This event may be external, such as a sensory or motor stimulus, or internal, as is a mental event, such as performing simple arithmetic. Cortical ERPs are the result of the generation of field potentials in the brain that originate from the spatial and temporal summation of excitatory and inhibitory post-synaptic potentials produced at the membranes of nerve cell bodies and dendrites in the cortex. This activity changes rapidly over time and has a spatially extended field. It may be recorded from the scalp or directly from the cortical surface and can be extracted from the continuous EEG by means of averaging and digital filtering. It is usually recorded with a temporal resolution in the order of a few milliseconds and is recorded from multiple locations. ERPs may be recorded in either the time or frequency domains, but this thesis will focus on ERPs recorded in the time domain.

ERPs are a non-invasive method of measuring brain activity during cognitive processing. The transient voltage fluctuations, which make up the components of the ERP, are assumed to be time-locked to the stimulus onset (e.g. the presentation of a word, a sound, or an image), though in certain circumstances this assumption may not hold true. Each component reflects brain activation

associated with one or more mental operations. In contrast to behavioural measures such as error rates and response times, ERPs are characterized by simultaneous multi-dimensional measures, such as polarity (negative or positive potentials), amplitude, latency, and scalp distribution. So by measuring the time it takes for an ERP to occur after presentation of the stimulus, and by taking recordings from several areas of the brain, it is possible to determine the sequence and timing of the specific areas activated within the brain. Therefore, ERPs can be used to distinguish and identify psychological and neural processes involved in complex cognitive, motor, or perceptual tasks.

2.1.2 ERP characteristics common to multiple sensory modalities

While the ERP responses recorded depend heavily on the stimulus type and experimental protocol, there are certain types of responses or effects that are characteristic of more than one sensory system. Two of these that are of particular relevance to this thesis are described below.

2.1.2.1 Habituation

When an innocuous or irrelevant stimulus is delivered repeatedly at a constant rate and intensity, such as in a train of stimuli (see section 2.1.4), there is a gradual decrease in the strength of the cortical response. This phenomenon is known as habituation and it is thought to reflect an elementary learning process if it is not caused by fatigue, damage to the sensory system or refractory period (Thompson and Spencer, 1966). It plays an important role in protecting against sensory overload and in saving cortical resources of memory and attention for more important novel stimuli. Habituation has been shown to be impaired in some conditions, such as migraines (Ambrosini and Schoenen, 2006).

The most notable effect habituation has on ERPs is a decrease in the amplitude of the response. Short-term habituation is dependent on the interstimulus interval (ISI) within the stimulus train; the amplitude of the ERP will decline with a shortening of the ISI (Kekoni et al., 1997). This is also known as the rate effect. Therefore in a train of stimuli, the first stimulus will be the largest in amplitude, with successive decrease in amplitude with each response until a plateau is reached.

2.1.2.2 Effects of stimulus duration

Longer stimulus durations (greater than 100ms) will demonstrate short transient cortical responses to the onset and offset of the stimulus in both the visual and auditory systems. In addition to this there is a sustained shift in the baseline response, which lasts the duration of the stimulus. This component is called the sustained potential and is only clearly observed at stimulus durations greater than 300ms. The actual distribution and timing of each of these components are specific to the sensory system being activated. These duration effects can significantly alter the morphology of the waveform and this needs to be taken into account if the experimental design requires the comparison of ERP responses to stimuli of different durations. *On-off* and sustained potentials are covered in more detail in section 5.1.

2.1.3 Signal analysis

The ERP responses elicited to a single stimulus are quite small, $< 20\mu V$, when compared with deflections of an average EEG trace ($15\text{-}50\mu V$). Thus the ERPs are not readily discernible from the background brain activity that is not related to stimulus processing. In addition to this, other 'noise', both physiological

and non-physiological, can also be added to the ERP response and together these signals may mask the presence of the electro-cortical signal of interest. The measure of the amplitude of ERP signal at any point relative to the amplitude of the background noise is called the signal-to-noise ratio (SNR). It is usually written as S (signal)/N (noise) and expressed in decibels. When recording ERPs the aim is to maximise the SNR in order to obtain the clearest response possible. Two basic methods of doing this are time-domain averaging and digital filtering.

2.1.3.1 Time-domain averaging

To extract the ERP from the background activity and noise containing overlapping frequencies, averaging many epochs of the same ERP may be performed. This can lead to an enhancement of the SNR, by a factor of root N; N being the number of trials recorded (Rompelman & Ros, 1986). The number of responses that need to be averaged will depend on the level of background noise and the characteristics, such as amplitude, of the ERP being recorded. The level of noise also needs to be assessed within the frequency range of the ERP of interest. It requires fewer averages to record a slow potential, such as the contingent negative variation, than it does a P50 component of similar amplitude in an eyes closed condition where the noise from the background EEG is of a similar frequency of around 10Hz. One of the simplest methods of assessing noise level in a recording is by superimposing the subaverages of replicate trials before calculating a grand average (Picton et al., 2000).

Averaging will often produce lovely looking traces, but the question remains as to whether an ERP is actually present. This question is particularly important when trying to discriminate a difference between stimuli, such as the difference between the cortical response to standard stimuli and that of deviant

stimuli (see section 2.1.3). Therefore it is necessary to demonstrate that averaged ERP is significantly different from that which would be obtained by averaging the EEG without the ERP being present. The main method used in this thesis is one commonly used throughout the literature examining sensory discrimination. It is a mean amplitude analysis, which statistically compares the differences in amplitude between two waveforms over a predetermined time-frame (e.g. Baldeweg et al., 2002; Foxe et al., 2000; Molholm et al., 2002).

2.1.3.1.1 Assumptions underlying signal averaging

How closely the resulting average matches the single response will depend on a number of assumptions holding true (for review see K.M. Spencer, 2005). The first main assumption is that all significant portions of the response are equally time-locked and phase-locked (Rompelman & Ros, 1986a) with stable characteristics, such as amplitude and waveform morphology. Unfortunately this is not always the case. An ERP consists of a number of different components, some of which may be sensitive to different factors, such as attention, novelty or primacy (see section 2.1.3). Thus the amplitude and/or the morphology of an ERP may alter during a trial and thus the resulting average is only a gross picture of the neural processes elicited by the stimuli. One possible method of minimizing these effects is "outcome-related averaging" (Donchin and Lindsley, 1966) in which averaging is based on an overt performance measure, such as reaction time. A slower reaction time to standard stimuli may indicate a lapse in attention, which would result in a corresponding change in waveform morphology (most commonly decreased amplitude). Similar selective averaging may be done of initial responses or novel stimuli of replicate trials in order to examine the effects of primacy or novelty.

The second main assumption is that the ongoing EEG activity is entirely random and will average to zero (i.e. there is no persistently rhythmical pattern) (Misulis, 1994). But research shows that the EEG is not entirely unrelated to the ERPs, with the early components possibly reflecting some reorganization of the phase of ongoing rhythmical activity that is induced by the onset of a stimulus (Makeig et al., 2001) and non-stimulus-locked oscillations appearing that are related to information processing (Spencer & Polich, 1999). Thus it is inappropriate to assume the ongoing EEG activity is uncorrelated to the event-related activity. However experience shows that for most ERP research the background EEG will average out sufficiently to provide useful information, particularly when coupled with digital filtering (see section 2.1.2.2).

The third assumption that is made is that the above factors will remain unchanged throughout the duration of the test. Again this is not always the case, mainly as a result of fatigue and/or boredom of the subject. As a trial proceeds a subject's attention will flag, resulting in a change in amplitude or morphology of the waveform. The subject may also get bored or tired and the background EEG will change, resulting in the introduction of persistent rhythmical alpha or theta activity. The simplest method of resolving this issue is to provide breaks within the session and to keep the length of the trials to a minimum. Two or three shorter trials of the same stimuli may prevent subject fatigue/boredom and will also provide replicate subaverages allowing the researcher to assess the reproducibility of their findings and the amount of background noise.

Finally it is assumed that there is no latency variability (i.e. jitter) present in the stimulus presentation and that the stimulus characteristics remain constant for each of the averaged runs (Rompelman & Ros, 1986a). If the latency of an ERP

component varies, then the amplitude of this component in the average will be decreased and the morphology distorted (fig. 2.1). One possible reason for latency variability in an ERP response is imprecise stimulus presentation. Careful calibration of equipment is needed to ensure the latency of the stimulus presentation is consistent. Endogenous latency variability also is a possibility. Some components of the ERP may have inherent inter-trial variability, with one possibility being a slower recovery rate. Comparison of subaverages of trials may suggest components that are more variable and, if necessary and practical, slowing down the presentation rate may help to reduce endogenous latency jitter.

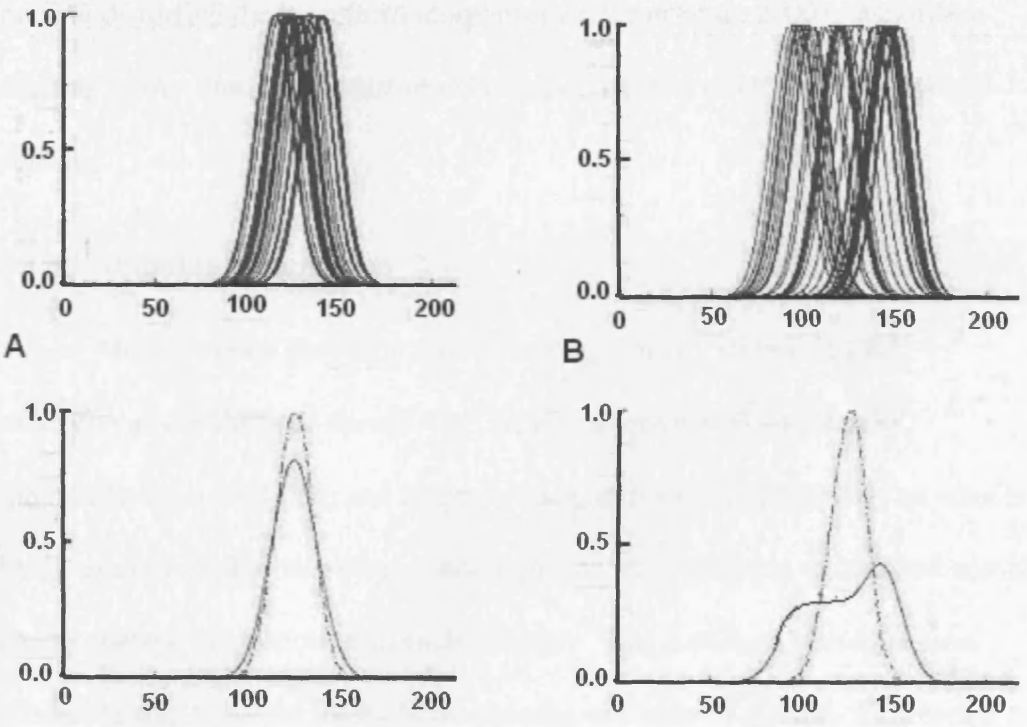


Figure 2.1: Examples of the Effects of latency variability. A. Latency jitter is ±10ms. B. Latency jitter is ±20ms. (top) Simulated component on each single trial. (bottom) The dotted line represents the simulated ERP component and the solid line is the average. (Based on K.M. Spencer, 2005) Note the decreasing amplitude and increasing distortion of the waveform as the latency jitter increases.

2.1.3.2 Digital filtering

Digital filtering is the simplest method for improving the SNR and does so by eliminating those frequencies in the recording that are irrelevant to the ERP being measured (Nitschke et al., 1998; Picton et al., 2000). Digital filtering is preferable to analogue filtering as the original data can be evaluated using multiple filter settings. This is an advantage as different components of an ERP may have different durations, i.e. P50 vs. P300, and different filter settings may optimally display different components (K.M. Spencer, 2005). In addition to this, digital filters can be set up so as not to alter the phase of frequencies within waveform and prevent distorting the waveform morphology (Picton et al., 2000). All offline filtering in this thesis were performed using digital filters set to prevent phase-shifting.

2.1.4 Stimulus presentation

Most common paradigms for presenting sensory stimuli in ERP experiments use trains of stimuli with the characteristics of the stimuli, interstimulus interval (ISI) and length of each train varying depending on what is being examined. The most basic paradigm is to present a train of identical stimuli and to average the responses to each stimulus. This paradigm is used in most clinical testing to assess the basic functioning of a sensory system. However a number of adaptations have been made in order to examine more specific cortical processes. The most pertinent to this thesis are the odd-ball paradigm and the standards-omitted paradigm.

2.1.4.1 The odd-ball paradigm

The odd-ball paradigm involves the presentation of an occasional deviant stimulus embedded in a series of more frequent standard stimuli, the two types of stimuli differing in some defined parameter, such as duration, frequency spectrum, location etc. In order to maintain the infrequent timing of the deviant stimulus, a pseudorandom presentation is used. This means that the order of the deviant and standard stimuli is randomised but with the constraint that no two deviant stimuli may be present in sequence. Historically, this is the paradigm that is most frequently used to study ERP components, particularly those associated with discrimination processes in the auditory, visual and somatosensory modalities (Picton et al., 2000).

The infrequent deviant stimuli will evoke a number of components not seen in the response to standard stimuli. These components include the P3a, P3b (section 2.2.1.2), and the mismatch response (see chapter 3). Odd-ball recordings can be performed during an active or passive situation and this will also dictate which components should be observed. During an active recording the subject must focus their attention to the stimuli and perform a task, such as button pressing or counting, when a specific stimulus is presented. During a passive recording the subject must ignore all the stimuli and will often be required to perform an unrelated task to draw their attention away from the stimuli.

2.1.4.2 Standards-omitted paradigm

Related to the odd-ball paradigm is the standards-omitted paradigm. The stimuli and trial presentation is the same as the odd-ball paradigm, but only the deviant stimuli are actually presented. This paradigm is useful in studying novelty effects and in differentiating between ERP changes in response to new afferent

elements of a stimulus and those in response to the actual change in stimuli (see discussion on mismatch responses, chapter 3).

2.1.4.3 Counterbalancing

Many ERP experiments use a repeated measures design (also known as within subject design) in which the ERPs of each subject are recorded in response to two or more different stimulus conditions. In order to avoid possible learning or habituation effects that may arise from the presentation order, the different stimulus conditions will be counterbalanced. Counterbalancing is used to avoid order effects and involves presenting to the subjects every possible ordering of the stimulus conditions. For example, in chapter 6 somatosensory event-related potentials are recorded in response to stimuli of different standard frequencies. If every subject received the high frequency standard stimuli first and the lower frequency ones second then there would be no way to know if the ERP responses to the lower frequencies were influenced by the previous exposure to the higher ones. Therefore the different frequency stimuli were counterbalanced, with half the subjects receiving the high frequency standard stimuli first and half receiving them second.

2.1.5 The inverse problem

In order to determine the location of the activity within the brain, advanced signal processing techniques are used to estimate the location of that activity's source from the electrical or magnetic signals recorded on the cortex surface or scalp. This is referred to as the *inverse problem.* The primary technical difficulty is that the waveform pattern recorded using electro-magnetic techniques may result from an infinite number of dipole source configurations and thus there is no

mathematically unique solution to the problem of inferring the numbers and locations of dipoles that, theoretically, produce the observed pattern of activity. Adequate solutions can be derived using models involving *a priori* knowledge of physiology and functional anatomy and the characteristics of the head, as well as localization algorithms. However the problem of finding the best solution to the inverse problem is in itself a topic of intense research.

2.2 Somatosensory event-related potentials

Somatosensory event-related potentials (SERPs) are a common and reliable method of studying the somatosensory system that has both research and clinical applications. SERPs obtained from stimulation of the median nerve are the most commonly utilized clinically and these are the responses of interest in this thesis. Several different waveform components have been described and these are loosely divided into 2 categories, early and mid/late components.

These individual components are labelled according to the polarity and latency of the maximal response but there tends to be a fair amount of discrepancy in the literature, particularly for the later components; this becomes particularly confusing when comparing results obtained using electrical stimulation versus mechanical stimulation or between scalp and subdural recordings. The component names used in this thesis reflect those that most commonly appear in the literature.

2.2.1 Main components of median nerve SERPs

The main components of the SERP in response to median nerve stimulation are summarized in table 2.1.

	ERP	Source and scalp distribution	Reference
Early components	N20	Maximal over contralateral cortex Thought to be a tangential current in posterior bank of the central sulcus area 3b	Allison et al., 1980; Allison et al., 1989; Baumgartner et al. 1991 Desmedt et al., 1983 Grimm et al., 1998; Kawamura et al., 1996 Mauguiere et al., 1983
	P30	Next most prominent peak after N20 Thought to originate from postcentral area 3b, or possibly motor cortex	
	P50	Robust response Anterior-posterior polarity reversal, also thought to originate from postcentral cortical areas Maximal over contralateral cortex	
Mid/Late components	N70	Small, inconsistent component Appears over middle and posterior scalp May reflect IPSPs occurring after initial action potential in SI cortex	Allison et al., 1989; Desmedt et al., 1977 Desmedt et al., 1983 Desmedt and Tomberg, 1991 García-Larrea et al., 1991 Goff et al., 1977 Hämäläinen et al., 1990 Hari et al., 1983 Hari et al., 1984 Josiassen et al., 1982 Kekoni et al., 1996 Näätänen, 1992
	P100	Great inter-individual variability and often embedded in other components Bilateral response with anterior-posterior polarity reversal originating in SII cortex on upper banks of Sylvian sulci Larger when stimuli is attended	
	N140	Broad scalp distribution Maximum amplitude at contra-lateral posterior hemisphere When stimuli is attended the maximum amplitude shifts anteriorly Thought to originate in SII and reflect activation of Brodmann area 46 and reciprocal interactions between posterior and prefrontal cortex and subcortical structures	
	N250/ P300	Attention related complex similar to the N2b-P3 complex of the auditory and visual systems. Evoked by infrequent and novel stimuli Most likely to have a fronto-central distribution	

Table 2.1: Summary of the main components of the cortical SERP in response to median nerve stimulation.

2.2.1.1 Early latency components

The early components depend largely on the characteristics of the stimulus and are resistant to cognitive factors and pharmacological interventions (Clark and Rosdner, 1973, Hume, 1979). These are often termed exogenous potentials and tend to be the most commonly used clinically as they are robust and easily recordable. Of these early components, only the P50 is of relevance in this thesis. Owing to the relatively low intensity of the stimulus and long analysis period used in the experiments discussed in the following chapters, the other components are only poorly observed if at all. The P50 component has been classified here as an early latency component owing to latency conventions (Misulis, 1994) but it is somewhat susceptible to cognitive factors (Desmedt et al, 1983). It is generated at postcentral cortical areas (Hari, 1984; Mauguière et al., 1983), most probably within the primary somatosensory cortex (Hämäläinen, 1990), and occurs contralateral to the side of stimulation.

2.2.1.2 Middle and late latency components

The mid/late components are more sensitive to the influence of cognitive factors, such as attention, and pharmacological interventions (Innocenti and Mazoni, 1972; Josiassen et al., 1982; Kekoni et al., 1997; Towe, 1966). These components are often termed endogenous and the P100, N140, and P300 are the ones of most relevance to this thesis.

The P100 has a broad scalp distribution and shows greater interindividual variability than the preceding components (Goff et al., 1977). It appears bilaterally over the parietal region, most probably with an origin within the secondary somatosensory cortices (Hämäläinen, 1990; Hari et al., 1984). It appears more distinctly in response to high frequency vibration than to low frequency vibration

or mechanical tapping (Hämäläinen, 1990). Several studies have indicated that the P100 is sensitive to experimental paradigm and psychological factors (Desmedt and Robertson, 1977; Goff et al., 1977). Larger P100 deflections are seen to attended, as opposed to unattended, stimuli (Desmedt et al., 1983; Josiassen et al., 1982) and similarly to novel stimuli (Kekoni et al., 1997; Kida 2004).

The N140 component follows the P100 and appears to be involved in passive attention and possibly in the maintenance of attention. It also has a broad distribution and appears with maximum amplitude over the contralateral post-central parietal region (Desmedt and Robertson, 1977). The N140 component can be elicited by attended and unattended stimuli (Kida et al., 2004); however the response to attended stimuli will have a maximum amplitude that is more anterior to that of the response to unattended stimuli (Josiassen et al., 1982; Kida et al., 2004). In addition to attention, the probability and ISI have also been shown to affect the amplitude of the N140 component, with increasing amplitudes associated with longer ISIs and decreased probabilities (Kida et al., 2004; Nakajima and Imamura, 2000). It is thought there may be several different generators of the N140 component that are likely to originate in the contralateral secondary somatosensory cortex (Hari et al., 1983, 1984, 1993) and reflect activation of Brodmann area 46 as well as reciprocal interactions between posterior and pre-frontal cortex and subcortical structures (Desmedt and Tomberg, 1989; Hämäläinen, 1990).

The P300 is an attention related component, similar to the visual/auditory P3, which seems to be elicited in active oddball or discrimination situations and has been proposed to index a neural system involved in attention and memory capacity. The P300 is most easily evoked in experiments where the subject actively attends

to rare or deviant stimuli (García-Larrea, 1991; Ito et al., 1992) and similar to the N140, the P300 will show an increase in amplitude associated with an increase in the ISI or a decrease in the probability of the stimuli (Nakajima and Imamura, 2000). Like the P3, there are two components; an early P300a component (around 300ms) that appears maximally over the central region in response to novel stimuli and habituates slightly with repeated trials and a later P300b component (around 350ms) that appears maximally over the parietal regions in response to the correct identification of a target stimuli (Bruyant et al., 1993; Yamaguchi and Knight, 1991). While both P300 components have a broad scalp distribution, they tend to consistently lateralize over the hemisphere contralateral to the side of stimulation (Bruyant et al., 1993; Kekoni et al., 1996). A supplementary study by Bruyant et al. (1993) demonstrated that the P300a component did not depend on the sustained attentional activity of the hemisphere contralateral to the target side, but would lateralize to the hemisphere contralateral to the actual stimulation. Thus they proposed that the P300a component reflected an automatic processing of deviant stimuli similar to that of the auditory and visual P3a.

2.2.2 Maturational changes of SERPs

The morphological, amplitude and latency changes seen in somatosensory electrophysiology during development reflect some of the same processes seen in the other sensory modalities, i.e. increasing conduction velocity in nerve tracts as a result of progressing myelination (Vecchierini-Blineau and Guiheneuc, 1979) and a possible increase in the efficacy of the synapses (Eggermont, 1986). However these factors are further complicated by the variations in physical growth between children and by the asynchronous maturation of peripheral and central segments of the somatosensory pathway (For review see Bartel et al., 1987; Gilmore et al.,

1985). Most developmental studies look at peripheral and early latency cortical responses. In general they have found a rapid decrease in latency and increase in amplitude in both peripheral and cortical response over the first year of life, which thereafter slows until about 4yrs of age (Cadilhac et al., 1986; Eggermont, 1988; Desmedt et al., 1973). At around 4 years median nerve conduction velocity does not significantly change, but there continues to be large changes in the somatosensory cortical responses, with a central conduction time, absolute and inter-peak latencies decreasing with increasing age until around 17 years (Allison et al., 1984; Bartel et al., 1987; Nishimura et al., 1986). The later cortical potentials, such as the P300, show a similar trend (for review see Segalowitz and Davies, 2004).

2.2.3 Electrical vs. Mechanical stimulation

The majority of previous studies have utilized electrical stimulation to evoke SERPs and this is the most common stimulus type used clinically (for review see Desmedt, 1988). One advantage of using this type of stimulus is that it bypasses sensory receptors and directly stimulates afferent nerves; thus the temporal dispersion in the afferent volleys arriving at the cortex is small and the resulting evoked potentials (EPs) are more distinct. However many people find the stimulus particularly uncomfortable or even painful, which often will lead to increased tension and muscle artefact. This in turn will increase the amount of background noise in the recording, which could obscure the cortical responses of interest (Bennett et al., 1980; Leandri et al., 1987).

A more natural alternative to electrical stimulation is mechanical, or vibrotactile stimulation of the skin. In the 1980s mechanical stimulation with rapid rise times (such as tapping and vibration) was tested (Larson and Prevec 1970,

Onofrj et al. 1999) and the SERP components were shown to closely resemble those elicited by electrical stimulation, though with a somewhat later latency and lower amplitude (Hämäläinen et al. 1990).

2.2.3.1 Vibrotactile stimulation

Vibratory stimulation provides a controlled means of stimulating distinct groups of skin mechanoreceptors (table. 2.2).

Mechanoreceptor	**Vibration Frequency (Hz)**
Merkel cells	< 10
Meissner Corpuscles	10 – 60 (max. 30)
Pacinian receptors	> 60

Table 2.2: The vibration frequency range at which the each mechanoreceptor is most sensitive (Johnson et al., 2000; Bolanowski et al., 1988; Vallbo et al., 1984; Johansson et al., 1982).

The information from each type of mechanoreceptor is then carried by anatomically and electrophysiologically distinct pathways from the periphery to area 3b of SI (Dykes et al., 1981; Torebjork et al., 1987). This separation persists through the input stage (area 3b) and secondary stage (area 1) of SI cortical processing (Friedman et al., 2004) with possibly some degree of segregated processing occurring at higher cortical levels (Harris et al., 2001). In addition, the secondary somatosensory cortex (SII) is most effectively activated bilaterally by high frequency vibration (Ferrington et al., 1980; Hämäläinen et al., 1988) with Pacinian afferents projecting more strongly to the SII than to the SI cortex (Fisher et al., 1983).

2.3 Conclusion

Event-related potentials are a very useful and powerful method for studying the cortical processing of sensory information. There are a large number of techniques and paradigms used in the recording of ERPs and these must be appropriate for the sensory modality being tested as the ones used will heavily influence the resulting ERPs. This is especially true of the somatosensory system, which, because of its large size and complexity of receptors and anatomical pathways, is one of the most difficult sensory systems to study. The type of stimuli and location of stimulation is particularly important to clarify when studying ERPs in the somatosensory system. For example stimulation of the leg will result in a different distribution of ERP responses from that of the arm, or using temperature stimuli will activate different pathways than that of vibration stimuli and this will result in quite different cortical ERP responses. This chapter has outlined the techniques and paradigms pertinent to the recording of median nerve somatosensory ERPs performed in this thesis.

Chapter 3: The mismatch process

3.1 Mismatch processing

Sensory information is of a transitory nature, therefore the integration across time; extraction of relevant information and decisions about where attention needs to be directed requires retention in the sensory memory for a short period of time (Cowan, 1984). The sensory memory (section 1.4.1.1) maintains a temporary history of the sensory environment and provides a means of monitoring the correspondence between a stored model and the incoming sequence of stimuli (Winkler et al., 1996). Mismatch processing occurs when there are deviations of the incoming sequence from the stored model. It can be measured using ERPs by subtracting the response to standard stimuli from that of deviant stimuli presented using an odd-ball paradigm (section 2.1.4.1). The resulting waveform is what is called the mismatch negativity (MMN). The MMN has been reported using auditory, visual and somatosensory stimuli.

The MMN is thought to provide an objective measure of the automatic, pre-attentive processing of perception and discrimination (auditory: Näätänen & Alho, 1995; visual: Stagg et al., 2004; somatosensory: Kekoni et al., 1997). Thus there is growing interest in using MMN as a possible clinical tool, as alterations in this potential are being characterized in a number of clinical conditions, such as dyslexia (Baldeweg et al., 1999; Schulte-Körne et al., 1998), Alzheimer's disease (Tale and Butler, 2006) and schizophrenia (Baldeweg et al., 2002; for a review, see Michie, 2001).

The majority of what is known about mismatch processing comes from studies of the auditory system. This work has led to the characterization and defining of the process and thus a significant portion of this chapter will focus on

the auditory MMN (aMMN) before reviewing what is known about mismatch processing in the other sensory modalities.

3.1.1 Characteristics of a mismatch process

Four main characteristics have been developed that define the mismatch process. These are all based on work done in the auditory system and have been used to identify similar processing within the visual and somatosensory modalities. The first is that mismatch processing is not simply the response of different neuronal populations responding to new afferent elements of the deviant stimulus but is generated by encoding processes within the brain (Näätänen, 1992). Thus it is not a change in particular physical characteristic of the novel stimuli that evokes the MMN, but rather a change of the regularity of the sensory input. The next characteristic of mismatch processing is that it is pre-attentive (Näätänen, 1992). The MMN is thought to reflect an automated process and as such can be recorded in the absence of attention, i.e. in experimental paradigms where the subject is asked to ignore the ongoing stimulus, usually by performing an independent distraction task. Thirdly, the mismatch process is independent of stimulus feature. It may be elicited by changes in any stimulus feature even when the changes just approximate the behavioural discrimination threshold (Amenedo and Escera, 2000). Finally the mismatch processing is sensitive to the magnitude of the sensory change. This is evidenced by the increase in the amplitude of the MMN when the deviants deviate more from the standards (Schröger, 1996).

3.2 The auditory mismatch negativity

The auditory mismatch negativity is an auditory ERP (AERP) elicited by an infrequent change in a stream of continuous, repetitive stimuli (whether tones or

phonemes) that occurs even in the absence of attention (Alho et al., 1992; Alho et al., 1998; Fischer et al., 1999; Giard et al., 1990; Mima et al., 1998; Näätänen et al., 1993; Paavilainen et al., 1991). The aMMN may reflect high temporal resolution in sensory discrimination processes in the time window of auditory sensory memory (Näätänen & Alho, 1997). It is also proposed that the MMN may underlie an attention switching signal that triggers a chain of cerebral events which leads to the effective orienting of attention towards the detected change (Näätänen, 1990; Näätänen, 1992).

3.2.1 Characteristics of the auditory mismatch response

The aMMN appears as a negative shift in the ERP beginning at around 100ms after an occurrence of a sound change and is between 100-200ms in duration. It overlaps other AERP components, such as the N2, and is best seen as a difference wave obtained by subtracting the ERP to standard sounds from the ERP to deviant sounds (for a review see Näätänen, 1992). The aMMN cannot be attributed to new non-refractory afferent elements activated by an occasional infrequent stimulus as it is not elicited by deviant stimuli when they are presented without the intervening standards, nor is it evoked by the first stimulus in the sequence or when interstimulus intervals are very long (Sams et al., 1985). In addition an aMMN was found in response to an occasional omission of the second tone of a closely paced tone-pair (Yabe et al., 1997). It has also been observed when there is a tone repetition in a sequence of steadily descending tones (Tervaniemi, et al., 1994). Thus it is proposed that the first standards presented in a stimulus block develop a memory trace representing many of the stimulus features, such as temporal aspects and sequence trends and if a deviant stimuli is presented while this memory trace is active then the aMMN is evoked (Näätänen, 2003).

The role of the aMMN in triggering an attention switching mechanism is most strongly supported by evidence provided in studies showing deterioration of task performance when task-irrelevant deviant auditory stimulation elicits an aMMN (see review in Escera et al., 2000). This occurs in both visual-auditory and auditory-auditory distraction paradigms (Escera et al. 2002; Shröger, 1996).

3.2.2 The effects of frequency and duration deviants on the aMMN

The physical features of a simple stimulus deviance, such as frequency and duration, can alter the latency and amplitude of the resulting aMMN response. Studies that have compared the aMMN response to frequency deviants with those to duration deviants have found significantly higher amplitudes and more stable waveforms in response to the duration deviants (Escera et al., 2002; Kathmann et al., 1999). It has also been shown that the aMMN response will increase in latency as the duration of the stimulus increases (Jaramillo, 2000) and will be absent or very low amplitude when long stimulus durations (around 1000ms) are used (Grimm et al., 2004).

3.2.3 Distribution of the aMMN

The aMMN is distributed maximally over the fronto-central scalp regions. This has been explained by bilateral sources in the temporal auditory cortices resulting in the summation of activity over the frontal-central scalp (Alho et al., 1998; Giard et al., 1995; Leväinen et al., 1996; Scherg et al., 1989).

In addition to the bilateral auditory cortex generators, there is a pre-frontal generator (Deouell et al., 1998; Giard et al., 1990; Jemel, 2002; Liasis et al., 2001) that occurs slightly later than the activation of the MMN in the auditory cortex (Rinne et al., 2000). This frontal aMMN has been proposed to play an important

role in initiating involuntary switching of attention towards a stimulus change outside the focus of attention (Giard et al., 1990; Näätänen & Michie, 1979; Schroger, 1996).

3.2.4 The aMMN in children

The aMMN appears very early in child development, with both a frontal and temporal component (Gomot et al., 2000; Liasis et al., 2001; Shafer et al., 2000) similar to that seen in adults. The aMMN morphology changes with age; the waveforms generally appear multiphasic and of longer duration in younger children, with the peak becoming more salient with increasing age (Gomot et al., 2000) in a manner consistent with other ERP components.

The aMMN has been observed in premature infants 30-35 weeks after conception (Cheour et al., 1998) and in newborns (Alho et al., 1990; Kurtzberg et al., 1995). Several studies in school-aged children concluded that the MMN response was like the typical adult MMN since it was very similar in peak latency, peak amplitude and fronto-central scalp distribution (Kraus et al., 1992). However, other authors have reported differences between child and adult MMN characteristics with higher amplitudes and/or longer latencies in children (Csepe, 1995; Korpilahti and Lang, 1994; Kurtzburg et al., 1995). There are also reports on reversed polarity in younger children compared with adults (Maurer et al., 2003) and inconsistent reports on differences in amplitude between the frontal and temporal aMMNs of adults and young children (Gomot et al., 2000; Martin et al., 2003) though the timing between the two components appear similar (Martin et al., 2003).

These inconsistencies make it difficult to interpret the meaning of any changes in the aMMN with maturation and suggest that maturation effects are

probably influenced by stimulation and experimental protocol. Comparison between the different studies is also further complicated by reported differences in aMMN generators to different types of stimuli, i.e. frequency and duration (Liasis et al., 2000). However a review of the literature suggests the following trends in the maturation of the aMMN from childhood to adulthood: 1. Latencies decrease with increasing age, at a rate of approximately 11ms/year between the ages of 4-11 years (Shafer et al., 2000). 2. Studies using complex speech stimuli or hard to discriminate stimuli report more similar peak latencies between adults and children (Csepe et al., 1992; Kraus et al., 1992). 3. Experimental paradigm appears to have has a greater influence on the elicitation of the aMMN in younger children than on older children or adults. 4. There is a high degree of inter- and intra-individual variability in the amplitude of the aMMN of children (Kurtzberg et al., 1995; Uwer and von Suchodoletz, 2000). 5. The aMMN is more strongly influenced by attention in children and this effect decreases with age. It is suggested that attention will facilitate the 'pre-attentive change detection mechanism' (Gomes et al., 2000; Wetzel et al., 2006).

3.3 The visual mismatch negativity

The visual mismatch negativity (vMMN) is the visual homologue of the aMMN. It appears as a negative shift that occurs over the period following the N1 component of the visual event-related potential (for review see Pazo-Alvarez et al., 2003). Some studies have shown two separate components, an initial negative component occurring between 100-200ms and a later negative component between 200-300ms (Czigler et al., 2006; Maekawa et al., 2005). It not nearly as well characterized as the aMMN, but work is ongoing. The following is a brief

overview of what is known about the vMMN and work supporting the premise the vMMN reflects a mismatch process.

3.3.1 Characteristics of the visual mismatch response

The vMMN has been shown to be evoked by changes in a range of different types of stimuli, such as windmill patterns (Maekawa et al., 2005), colored squares or bars (Stagg et al., 2004), colored checkerboard patterns (Czigler et al., 2006) and movement (Kremlacek et al., 2006), presented using an odd-ball paradigm. Some of these studies have used auditory or visual distractions tasks to draw the subject's attention away from the deviant stimuli, showing that a vMMN may be recorded in the absence of attention. (Czigler et al., 2002; Maekawa et al., 2005)

One of the biggest challenges in studying vMMN has been to rule out the exogenous effects of the stimulus characteristics and to control for selective habituation in order to ascertain that the vMMN in not just a response to the new afferent features of the deviant stimulus. Some studies have addressed this question, either by alternating the standard, deviant or target stimuli (Maekawa et al., 2005) or by attempting to standardize the adaptation state of receptors and neurons in the visual fields exposed to the deviant and standard stimuli (Czigler et al., 2002; Stagg et al., 2004). More recently, Czigler et al. (2006) used repetitive stimuli in a set sequence and determined that a vMMN was elicited by changes in the sequence of the repetitive stimuli and not by regular repetitions or regular stimulus changes.

3.3.2 Distribution of the vMMN

The vMMN has a broad distribution over the posterior part of the scalp and usually occurs maximally over the occipital and posterior temporal regions (Czigler

et al., 2005; Maekawa et al., 2006; Stagg et al., 2004). The two components may possibly have different distributions with the later component having a more parietal distribution (Maekawa et al., 2006). There is a significant dearth of published information regarding the possible lateralization of the vMMN or on putative cortical sources.

3.4 The somatosensory mismatch process.

As this thesis focuses on the somatosensory system, this overview will examine the literature concerning somatosensory mismatch processing in more detail than was done for the visual system.

3.4.1 Characteristics of the somatosensory mismatch response

Event-related potentials to stimulus detection within the somatosensory system have been well documented, but only a few studies have investigated stimulus discrimination and possible mismatch processing. In a magnetoencephalography study using electrical stimuli, early contralateral components were found in the primary somatosensory cortex (SI) and contra- and ipsilateral responses in the secondary somatosensory cortex (SII). The later SI responses were enhanced by rarely presented electrical stimuli during active and passive attention paradigms, while the SII responses were only enhanced during active attention paradigms (Mima et al., 1998). This suggests that processing in the SI region may occur at an early stage. A limited number of investigations into pre-attentive somatosensory processing, using different types of stimulation, have reported a comparator mechanism in the somatosensory modality (Akatsuka et al., 2005; Kekoni et al., 1997; Kida et al., 2001; Shinozaki et al., 1998) with properties similar to that of the auditory mismatch negativity.

Kekoni et al. (1997) used a 300ms vibrotactile stimulus to compare standard somatosensory responses with either a frequency or position deviant. They reported an extra negativity over the fronto-central regions, occurring between 100-200ms after stimulus onset. A subsequent study by Shinozaki et al. (1998), using 0.2ms electrical stimulus and a positional deviant, reported an enhanced N60 component followed by a fronto-central positivity occurring between 100-200ms. In 2001, Kida et al. performed a similar experiment, using electrical stimulation with position changes between the middle and index digits. They also found an enhanced N60 component, but did not find any positivity between 100 and 200ms. More recently, Akatsuka et al. (2005) recorded SERPs elicited by temporal changes in two-point discrimination using a 0.1ms electrical stimulus. They also found a N60 enhancement and a positivity between 100-200ms similar to that reported by Shinozaki et al. (1998). However the positivity was only seen when the difference between the standard paired stimuli was longer than that of the deviant. In each of these studies the stimuli was to be ignored and a distraction task used to draw the subjects' attention away from the stimuli, thus indicating pre-attentive processing.

Both Shinozaki et al. (1998) and Kekoni et al. (1997) performed experiments in which the deviant stimuli were presented in a standards-omitted paradigm (section 2.1.3.2) in order to ascertain whether or not the above negative shift in the standard response was due to physical changes in the somatosensory stimuli or due to changes in the regularity of the stimulus presentation. In both studies, when the responses from the standards-omitted paradigm were compared to the deviant responses obtained in the odd-ball paradigm (section 2.1.3.1) they found that the responses from the odd-ball paradigm showed a negative component

that started earlier than the N140 component and that this component was more lateralized. This suggests a change-related response to a specific sensory process akin to the aMMN.

3.4.1.1 Cortical generators of the sMMR

FMRI, SERPs and MEG studies suggest that the somatosensory mismatch response (sMMR) originates in the parietal region, most likely in the primary and/or secondary somatosensory cortices (Huang et al., 2005; Kekoni et al., 1997; Stoeckel et al., 2003). In addition, MEG and fMRI studies of tactile discrimination tasks have also suggested the involvement of the anterior cingulate and dorso-lateral prefrontal cortices (Huang et al., 2005; Stoeckel et al., 2003). This is supported by neuronal recordings in monkeys, in which somatosensory discrimination was reported to show involvement of both somatosensory (Hernandez et al., 2000; Zhou and Fuster, 1996) and inferior prefrontal (Romo et al., 1999) regions.

3.5 Summary

In summary, the literature supports the existence of a somatosensory mismatch response that is similar to those described in the auditory and visual systems. Mismatch processing in the auditory and visual systems is reflected by a negative shift in the deviant response, which gives rise to the MMN. A similar component (the sMMN) has also been reported in the somatosensory system. However there are a number of discrepancies in the latency and morphology of the sMMN. The latencies vary between 60ms, considerably earlier than those reported for the other two modalities, and 100-200ms, which is consistent with the MMN reported in the other modalities. In addition a positive component following the

sMMN has been reported in some studies and this component appears unique to the somatosensory system. The experiments described in chapters 5, 6 and 7 aim to address the inconsistency in the latency values of the sMMN and will try to further characterize this positive component.

Chapter 4 : Evoked potential recording – Methodology

4.1 Introduction

When recording event-related potentials, background cortical activity and other 'noise', both physiological and non-physiological, is added to the signal and one of the simplest and most common way of removing these extraneous noise signals is by averaging (see section 2.1.2.1). In using the averaging technique, a number of assumptions are held to be true and included in these are that the timing of the stimulus presentation is consistent and that the characteristics of the stimuli remain constant throughout the run (section 2.1.3.1.1). The two experiments described in this chapter were designed to ascertain if these assumptions were accurate by ensuring minimal latency variability in the stimulus presentation and by ensuring that the stimulator providing the somatosensory vibratory stimulus was able to provide a stable, consistent stimulus under experimental conditions.

4.2 Experiment 1 - Testing latency variability in the stimulus presentation

4.2.1 Background

The stimuli used in the experiments described later in this thesis are presented via a computer program. Depending on their specifications individual computers will perform differently in response to the demands of the programs and delays in stimulus presentation may occur, particularly when working through multitasking operating systems such as Windows™, as this program does. In addition, the program also uses the sound card to send a sine wave impulse that triggers the stimulator (electro-mechanical shaker or speaker). It simultaneously

sends a trigger signal to the Neuroscan recording system via the parallel port so that the time and type of stimulus will be recorded in conjunction with the physiological data (see fig. 4.1, section 4.2.2). This trigger signal is the basis of off-line averaging. There is always a discrepancy between the trigger signal sent via the parallel port and the stimulus signal sent through the sound card as a result of an internal latency delay in the sound card. This latency delay is usually documented in the specifications of the sound card and the trigger to stimulus delay should be consistent and thus will not affected averaging. However if either this delay or the stimulus output signal is too variable then the averaged cortical response waveform will be compromised, particularly with respect to amplitude measurements, and the results unreliable (section 2.1.3.1.1).

This experiment tested the discrepancies between the trigger and stimulus output signals for three computers with different specifications to determine which was the most consistent and reliable in presenting the stimuli to be used in subsequent experiments.

4.2.2 Methods

The program to be used to present the stimuli was loaded onto each computer and tested to ensure it was running correctly. It was designed to present stimulus in an oddball paradigm with an interstimulus interval of 1000ms. Initially each computer was connected to a 2 – channel oscilloscope (465B Tektronix) and the stimulus presentation program was run. The output signals from the parallel port and external BNC stimulus trigger cable were monitored to gain an idea of their amplitudes. The digital output cable was used rather than the stimulator itself so that the setup would share the same ground. To quantify the onset latencies of the trigger and stimulus signals, each computer was, in turn, connected through

both the parallel port and the stimulus trigger cable to the Neuroscan recording system via the headbox and Synamps amplifiers (fig. 4.1). To record through the headbox a voltage divider circuit was required, as the output signals from the parallel port were in the region of 5V when measured using the oscilloscope. Based on a V_I of 15V (a 10V safety margin over the output signal recorded from the parallel port), and a R_2 of 5KΩ (approximately scalp impedance), the following calculations were made to determine the value of second resistor needed to drop the voltage to 5mV, a value easily tolerated by the amplifiers.

$V_O = V_I (R_2/R_1+R_2)$

$5 \times 10^{-3} = 15 (5/R_1+5)$

$0.33 \times 10^{-3} R_1 + 0.33 \times 10^{-3} (5) = 5$

$0.33 \times 10^{-3} R_1 + 1.6 \times 10^{-3} = 5$

$R_1 = 15151\ K\Omega = 15.15M\Omega$

V_O – voltage output, V_I – voltage input, R_1 – Resistor 1, R_2 – Resistor 2

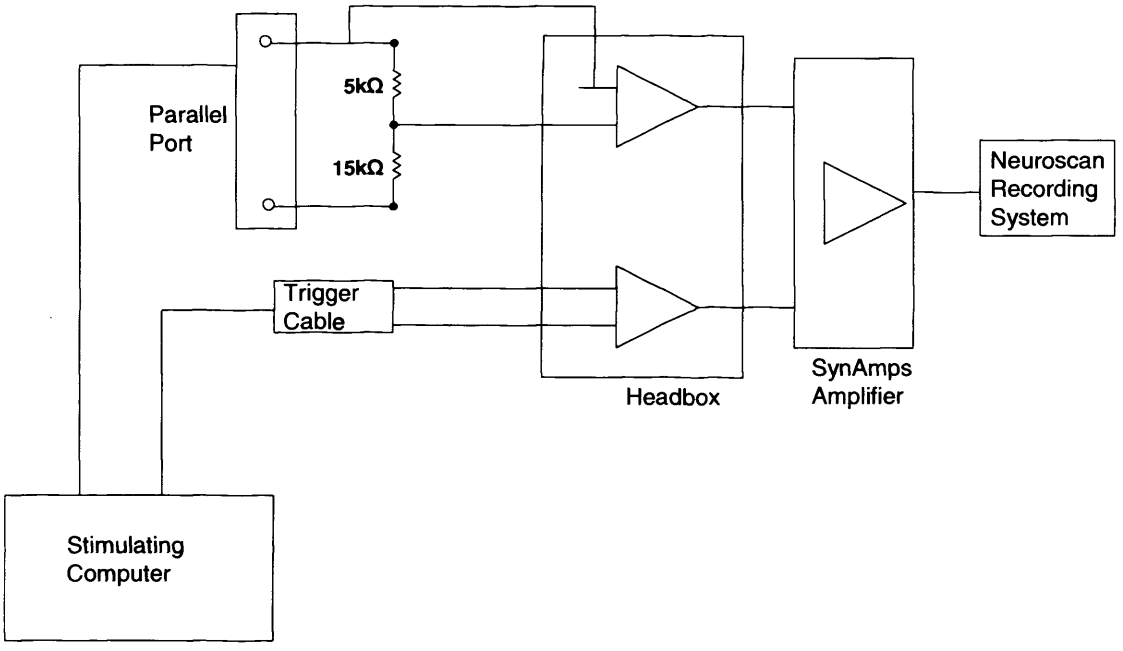


Figure 4.1: Schematic diagram of circuit used to test and record discrepancies between stimulus trigger and output signals.

The stimulus presentation program was run until a minimum of 40 signals was recorded. These signals were then analysed further offline. The continuous recording was separated into 1000ms epochs and the onset latencies of the trigger and stimulus output signals were measured. The internal variability in onset latency, and the difference in the onset latency between trigger and stimulus signals, were analysed for each computer.

4.2.3 Results

The onset latencies for the trigger and stimulus output signals are shown in appendix 4 and the results are summarized in Table 4.1. Out of the three computers, number 2 showed the most inconsistent onset latencies; with trigger onset latencies ranging between 84-300ms and stimulus onset was between 108 – 322ms. However the difference between the trigger and stimulus outputs was fairly consistent at 21.2 ±3.2ms. Computer number 3 showed the most consistent onset latencies, with the trigger and stimulus signals ranging between 192 – 196ms and 206 – 212ms respectively. The difference between the stimulus and trigger onset latencies was the most consistent, with an average of 15.2 ±1.3ms.

Computer	Signal	Range (ms)	Mean ±SD (ms)
1	Trigger	186 – 202	193.6 ±4.3
	Stimulus	204 – 220	214.1 ±4.4
	Difference	12 – 26	20.5 ±3.4
2	Trigger	84 – 300	185.5 ±101.6
	Stimulus	108 – 322	206.7 ±101.4
	Difference	14 – 28	21.2 ±3.2
3	Trigger	192 – 196	193.4 ±1.1
	Stimulus	206 – 212	208.6 ±1.4
	Difference	14 – 18	15.2 ±1.3

Table 4.1: Summary of the onset latencies for the stimulus and trigger output signals.

4.2.4 Conclusions

The simple tests performed above showed a clear difference between the three computers in their ability to consistently present a stimulus with minimum variability in onset latency. To gain reliable and interpretable results in ERP experiments it is vital to minimize the amount of jitter in the cortical responses if averaging techniques are used to improve SNR (section 2.1.3). One of the easiest and most simplistic ways of doing this is to ensure the stimulus onset occurs at the same time on each presentation. The huge variations in the onset of the stimulus presentation from computer 2 made it completely unsuitable for our experimental design despite a fairly consistent trigger to stimulus delay. Computer 1 showed a considerably more consistent stimulus onset than computer 2 and had a consistent trigger to stimulus delay. However computer 3 was observed to have the least amount of variability in both stimulus onset and trigger to stimulus delay and thus this computer will be used in subsequent experiments to present the stimuli. The average trigger to stimulus delay was 15ms, indicating that the stimulus occurred 15ms after the marked response on the Neuroscan recording system. Therefore a 15ms correction reflecting the trigger to stimulus delay will be taken into account when reporting latency values in this thesis.

4.3 Experiment 2 - Performance of the vibration stimulator under experimental conditions

4.3.1 Background

The somatosensory vibration stimulus used in this study was delivered via an electromagnetic shaker. Electromagnetic shakers are force generators or transducers that use an electromagnet to create the force and vibration. One feature

of this type of stimulator is that the dynamic force applied is dependent on the applied resistance, with the force decreasing as the resistance increases (LDS datasheet 16.00). This introduces the possibility that movements or variations in hand weight will alter the force being applied to the subject. As a result, responses to intentional changes may be masked or distorted by frequent unintentional alterations in stimulus intensity resulting from normal variations in subject behaviours that are difficult to control.

The aim of this experiment was to determine if the small changes in load on the vibratory stimulator would sufficiently alter the intensity of the stimulus such that it will significantly distort or mask the resulting somatosensory evoked potentials.

4.3.2 Subjects

All subjects in this experiment, and subsequent experiments reported in this thesis (excluding the intracranial studies), were healthy with no reported history of psychiatric or neurological disorders, or of injury to the central or peripheral nervous system. Handedness was ascertained using the Edinburgh handedness inventory (Oldfield, 1971, appendix 5) and informed consent was obtained from each subject. This project was approved by the Great Ormond Street Hospital for Children/Institute of Child Health Research Ethics Committee (Ref. no. 02-NR-10).

In this study, the subjects consisted of nine adults (4 males, 5 females, all right handed), aged between 23-38yrs.

4.3.3 Methods

4.3.3.1 Stimulus

The trials consisted of bursts of vibration that were 20 ms in duration and 200Hz in frequency, with an interstimulus interval (ISI) of 1000ms.

4.3.3.2 Stimulus construction and delivery

An electromechanical shaker (Ling Dynamic systems 200 model) was employed to generate the vibration stimulus. An impedance head (Bruel and Kjaer, type 8001) containing a force transducer (appendix 6) was used to monitor the dynamic force of the stimulus.

A sine wave signal of the desired frequency, duration and amplitude was generated using 'Cool Edit 2000' (Syntrillium) software and saved as a .wav file. This was then incorporated into a 'Presentation' (version 9.1, Neurobehavioural Systems) program that dictated the parameters of the experiment, which included the stimulus .wav file to be presented, the number of stimuli in the run and the interstimulus interval. The sine wave signal was sent to a power amplifier via the sound card of the computer (Soundmax Integrated, HP d330D/P2.4). The signal was then transmitted to the oscillating coil of the shaker to provide the vibration stimulus, which was monitored by the impedance head. The stimulus was applied via a 'T-bar' screwed into the top of the impedance head. The oscillating coil of the shaker was at the zero phase point at stimulus onset, always rising in the positive direction. This facilitated the synchronous activation of fibres in the fingertips and minimizes 'jitter' of the cortical evoked potentials.

4.3.3.3 Experimental procedure

During the recordings, subjects sat in a comfortable chair and were asked to watch a self – chosen video placed 1.5m away. The video was used to draw the subjects' attention away from the stimuli, to minimize eye movements and was set at sufficient volume to mask any noise made by the oscillating coil of the stimulator. The right forearm and wrist were immobilized in a vacuum cast in order to support the hand and minimize movements. Vibration stimuli were applied to the digits 2 and 3 of the right hand as it selectively stimulates the median nerve. Two trials of 100 stimuli were delivered to each subject.

4.3.3.4 Continuous EEG and Force Recording

The equipment used for recording the dynamic force of the stimulus and ongoing continuous EEG are outlined in fig. 4.2.

Force and continuous EEG data were recorded, via a headbox and 'SYNAMPS' amplifiers, by the Neuroscan recording system (software version 4.2). The amplifiers were set to amplify at x12500 with a bandpass of 0.05-200Hz and a sampling rate of 500Hz. The signal from the impedance head had to be stepped down to allow the force data to be recorded.

Continuous EEG data was collect using forty-five Ag/AgCl electrodes that were applied based on a modified version of the International 10-10 system, with the highest density placed over the central third of the scalp (fig. 4.3). During the recording the reference was placed at POz and the ground at FPz'. The data was analysed further offline.

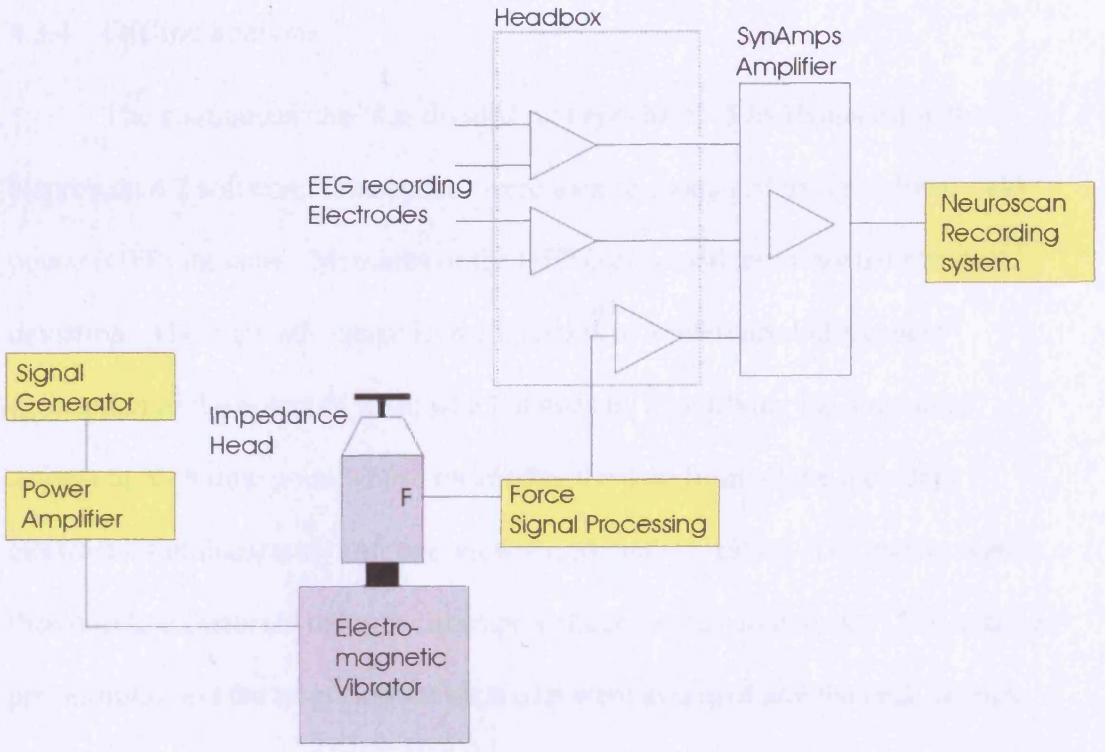


Figure 4.2: Block diagram of equipment set-up

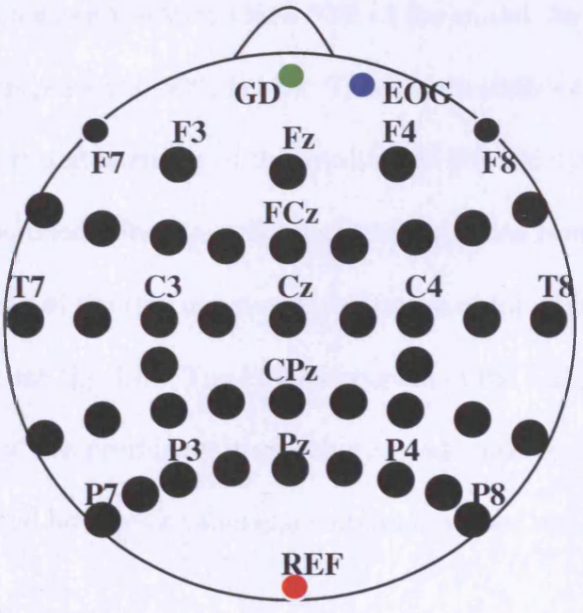


Figure 4.3: Schematic representation of the placement of the scalp electrodes used for recording ERPs in this thesis.

4.3.4 Offline analysis

The continuous data was divided into epochs of -5 to 150ms using the Neuroscan 4.2 software. The epochs were then re-montaged using a global field power (GFP) measure. Measures of the GFP correspond to the spatial standard deviation. The main advantage is that it results in a reference independent description of the potential field; which it does by quantifying the amount of activity at each time point while considering the data from all the recording electrodes simultaneously (for overview see Skrandies, 1990). The epochs were then baseline corrected using the average voltage calculated between -5ms and 0ms pre-stimulus and the responses for each trial were averaged and the peak latency and amplitude analysed using analysis of variance (ANOVA).

Then, for each subject, the force and corresponding cortical response of each of the two trials were divided into high and low force cohorts (A & B) based on the force amplitude at which 50% of the stimuli had a force amplitude value above this point and 50% below. These were separately averaged and the amplitudes and latencies of the resulting SERP and dynamic force wave-forms were examined. Force amplitudes were measured from the peak of the first upward to the peak of the first downward deflection of the averaged force wave-forms (for example see fig. 4.4). The P50 component of the SERP was chosen for analysis because it was prominent in all subjects and could be reliably measured. Peak latency and both peak and mean amplitude values were obtained.

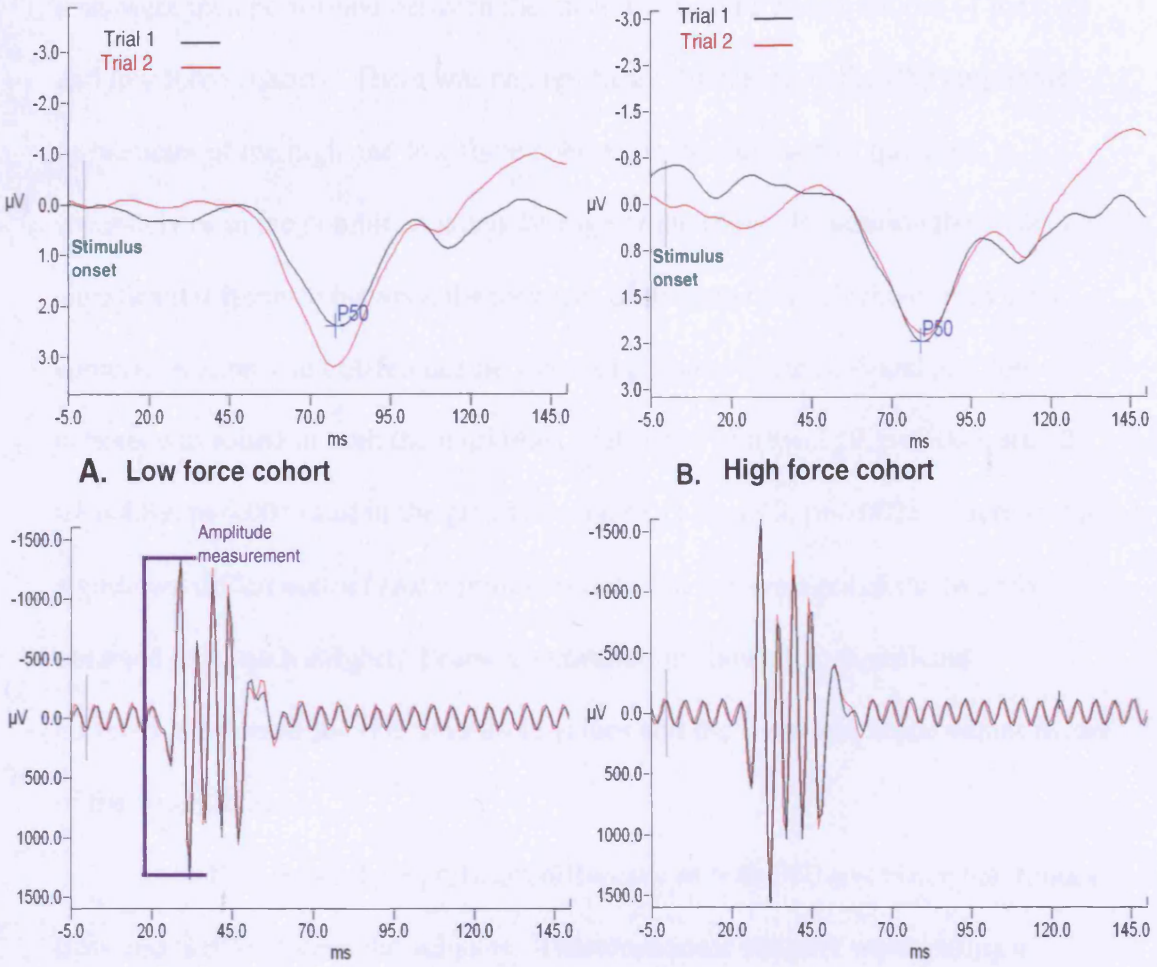


Figure 4.4: Example of the averaged outputs for one subject. The above waveforms are the P50 cortical responses and the lower waveforms represent the average dynamic force of the stimulus for each trial. Peak to peak measurements of the first deflection were used in the analysis. P50 measurements taken from CP3.

4.3.5 Results

Prior to division into the high and low force cohorts, ANOVA showed no significant difference within or between the subjects in either the force or the P50 amplitude or latency. Following division into the two cohorts, ANOVA (using the factors cohort, P50 amplitude, P50 latency, force amplitude, force latency) showed a significant main effect of cohort with significant interaction with P50 and force amplitudes ($F(1,2)=98.68$, $p=0.009$; P50 amplitude interaction: $F(1,30)=7.65$, $p=0.011$; force amplitude interaction: $F(1,30)=8.32$, $p=0.008$). Paired sample t-

tests were then performed between the mean force and P50 amplitudes of the high and low force cohorts. There was no significant difference in the P50 amplitudes or latencies of the high and low force cohorts; in neither each of the trials separately or in the combined grand average of the trials. In addition there was no significant difference between the averages of the two trials obtained from each subject. A significant difference between amplitudes of the high and low force cohorts was found in both the individual trials (trial 1: $t(8)=3.19$, $p=0.009$; trial 2: $t(8)=4.89$, $p=0.001$) and in the grand averages ($t(17)=4.63$, $p=0.002$). There was no significant difference in force amplitudes between the averages of the two trials obtained from each subject. Pearson's correlation showed no significant correlation between the P50 amplitude values and the force amplitude values in any of the conditions.

ANOVA showed a significant difference in both P50 and Force amplitudes (low and high) between the subjects. Therefore some subjects were getting a significantly different force. However while Pearson's correlation showed a significant correlation between the high and low amplitude of the force ($r=0.942$) and separately between the high and low amplitudes of the P50 component ($r=0.899$) there was no significant correlation between the P50 amplitude values and the force amplitude values.

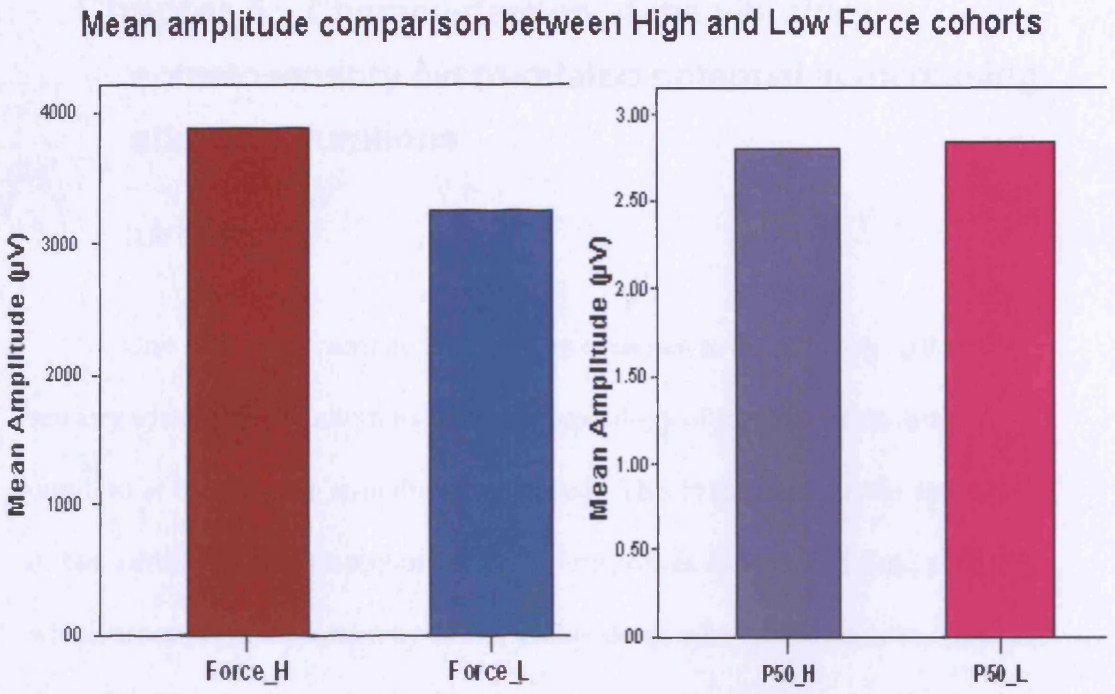


Figure 4.5: A graph showing the mean dynamic force and P50 amplitude values for the high (H) and low (L) force cohorts. There was a significant difference between the cohorts in the dynamic force being applied to the fingertips ($p<0.01$) but no significant difference in the resulting P50 cortical responses.

4.3.6 Conclusions

This study has shown that the small, but statistically significant variations in the force resulting from normal variations in subject's behaviour do not significantly affect the morphology, latency or amplitude of the P50 component of the vibratory SERP.

These results support the use of this technique within both clinical and experimental environments. It is less uncomfortable than electrical stimulation, it allows for easier manipulation of stimulus and it provides a controlled means of stimulating distinct groups of skin mechanoreceptors. Most pertinent to this thesis, variations in stimulation force did not distort the ERPs in this experimental design and thus this stimulation technique is valid for use in subsequent experiments.

Chapter 5: Characterization of the vibratory somatosensory event-related potential at increasing stimulus durations

5.1 Introduction

One ERP characteristic that appears common to the auditory and visual sensory systems is the alteration of the morphology of the waveform as the duration of the eliciting stimulus is increased. This is the result of the appearance of two additional ERP components, the *off*-responses and the sustained potential, which are usually subsumed by earlier components when short stimulus durations are used. The duration of a stimulus is an important component of sensory information and these temporally sensitive components may reflect the underlying cortical mechanisms responsible for determining the beginning, end and length of a stimulus. To date these responses have only been reported in the auditory and visual systems of humans; however it is plausible that similar mechanisms may exist in the somatosensory system.

5.1.1 Cortical responses to long duration auditory and visual stimuli

5.1.1.1 *On*- and *off*- responses

Short transient cortical responses to the onset and offset of a sensory stimulus have been reported for both the visual and auditory systems. These *on*- and *off*-responses tend to resemble each other with dipoles of similar distribution and direction (Noda et al., 1998; Pantev et al., 1996). However the *off*-response tends to be smaller and is more difficult to obtain as it is often subsumed by earlier waveform components. It requires stimulus durations of greater than 300ms to optimally record the *off*-response in these two sensory modalities (Crevits et al.,

1982; Hari et al., 1997), although auditory *off*-responses have been observed with durations as short as 100ms (Clynes, 1969; Tietze, 1979).

In the auditory system, dipole measurements using MEG have suggested that the *on*- and *off*-responses have different sources, with the *off*-response appearing anterior to the *on*-response (Hari et al., 1997; Joutsiniemi et al., 1989; Pantev et al., 1996). A more recent MEG study has reported a superior shift in the location of the *off*-response, but noted that at the frequency most closely resembling those used in the earlier studies, there was a tendency towards a more anterior shift. Thus they suggested that the distribution of the *off*-response may be dependent on other characteristics of the sound, such as frequency (Noda et al., 1998). Overall, the auditory *on*- and *off*-responses appear to have separate sources with closely located or overlapping distributions. Thus it is concluded that these two responses arise from closely related systems that heavily influence each other and are part of an inter-dependent, complex network.

On- and *off*-responses in the visual system have been less well characterized, but published data show a similar response pattern to that of the auditory system. As seen for the auditory responses, the visual *on*- response is composed of more than one component, CI/CII with cortical generators in separate regions, BA18 and BA17 (section 1.2.3.1) respectively (Maier et al., 1987). ERP studies show the *off*- response to have a similar distribution to the C1 component of the onset response and it is thought to have a cortical generator in the same region (Parker et al., 1982).

5.1.1.2 The sustained potential

In addition to the *on*- and *off*-responses, a sustained potential has also been reported in response to a prolonged stimulus. This has been observed in both the

auditory and visual sensory systems and has characteristics and distribution distinct from the transient *on*- and *off*-responses, suggesting it is part of a separate, though probably related, cortical network.

In the auditory system, sustained potentials were first reported by Köhler et al. (1952; Köhler and Wegener, 1955) and they described a sustained negative shift occurring maximally over the fronto-central regions of the scalp. Later studies examined the relationship of the auditory sustained potential to different stimulus parameters and determined that is was distinct from the contingent negative variation (CNV). In particular it could, unlike the CNV, be recorded in the absence of attention and during sleep. (Keidel, 1971, Picton et al., 1978a)

It has only been comparatively recently a similar sustained potential has been reported in the visual system and there are only a limited number of studies describing the characteristics of this response. It is seen with stimulus durations greater than 300ms and its persistence is dependent on the duration of the stimuli. It appears to originate in the calcarine cortex, more topographically similar to the CII *on*- response (Huettel et al., 2004)

5.1.2 Cortical responses to the temporal characteristics of somatosensory stimuli

In the somatosensory system there is electrical evidence of individual on-off neurons in the somatosensory cortex of monkeys (Sur et al., 1984), but to date there have been no reports of an *off*-response recorded from human subjects. One study by Hari (1980) reports a large negative sustained potential over the vertex and bilateral parietal areas in response to a 600ms vibrotactile stimulus delivered to the back of the hand. Unlike the sustained potentials reported for the visual and auditory systems, this one occurred later, 700ms, after stimulus onset and was only

clearly seen with the first stimuli, almost completely disappearing with stimulus repetition.

Possible reasons for the paucity of studies may lie with the short duration electrical stimulation most commonly used in the study of somatosensory evoked potentials (SEPs) and in the fact that the *off*-response requires more particular stimulation conditions than other transient potentials. It has only been relatively recently that mechanical and vibration stimulation have been used to investigate SERPs. Two studies recorded SERPs in response to a 300ms vibrotactile stimulus to the fingertips but no *off*-response was reported (Kekoni et al., 1996; Hamalainen et al., 1990). As mentioned previously, Hari (1980) used longer 600ms vibrotactile stimulation to record SERPs and reported a sustained potential, but not an *off*-response. As the *off*-response is considerably smaller than the *on*-response; recording it is more difficult and it is possible that the recording conditions were not optimal in the above experiments. Only a small number of averages were obtained with a correspondingly low SNR and it is possible that the stimulation site was not ideal and that the denser, smaller receptive fields of the fingertips could provide a stronger more easily recorded cortical response.

5.1.3 Aims of this study

The literature suggests that it is likely that the somatosensory system would have a mechanism for detecting the onset, offset and duration of a tactile stimulus, however studies specifically examining SERPs in response to different durations have not been reported. In this study somatosensory evoked potentials were recorded to a range of stimulus durations using a high frequency vibration applied to the fingers. The aim was to determine the presence of *on-off* responses similar to those reported for the auditory and visual modalities using scalp recordings. The

findings were examined in more detail in a case study using intracranial subdural electrodes.

5.2 Subjects

5.2.1 Experiments 3 and 4 – scalp recordings

A group of 10 subjects participated in the experiment (experiment 3: ages 22-36 years, 6 males; experiment 4: ages 19-40 years, 5 males) and all were right-handed.

5.2.2 Experiment 5 – intracranial recordings

A child with a pre-frontal tumour and resultant refractory epilepsy was undergoing pre-surgical invasive monitoring to assess the epileptogenic zone and areas of functional cortex were studied. This was done with hospital ethical approval and parental consent. The patient was an otherwise normal 14 year old girl with seizure onset at 8 years of age. She has had multiple seizure types, but her most common manifestations are spasm like movements with an ongoing indescribable feeling that often has a right side emphasis. Consciousness is preserved during these events. Magnetic resonance imaging showed a lesion over the left pre-frontal region. A sub-dural platinum electrode array (SEA) with 20 contacts was placed over the left sensory/motor strips and 2 6-contact electrode strips were placed over the lateral frontal cortex (fig. 5.1). None of the contacts were placed over the lesion owing to significant surgical risks at the time of implantation. Before surgical implantation a MRI scan was taken and was used to construct a three dimensional image of the patient's skull and cortex. This 3D-computer image was then co-registered to the patient's skull by obtaining a number of scalp co-ordinates using the Image Guidance System (IGS). A post-surgical

computerized tomography scan was obtained showing the placement of the contacts against the skull. Using the IGS, the 3D position of individual contacts were obtained and superimposed on the 3D reconstruction of the cortex. This confirmed the location of the contacts on the cortex.

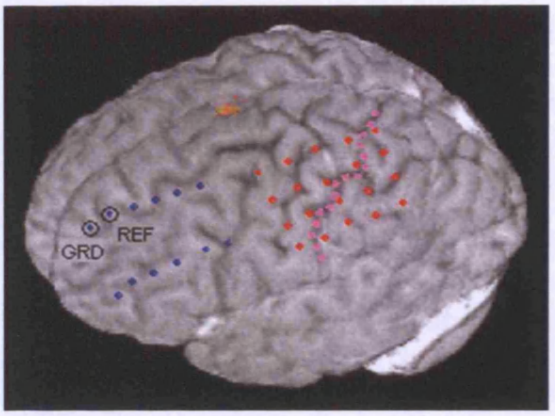


Figure 5.1: MRI reconstruction showing the placement of the sub–dural contacts used in experiment 5.

5.3 Methods

5.3.1 Experiments 3 and 4 – Scalp recordings

The methods of SERP recording and of stimulus construction and delivery are described in section 4.3.3.2.

5.3.1.1 Experiment 3

The subjects were tested in a single recording session lasting 2hrs with a 10 minute break in the middle. The recording session included six runs, each of which consisted of 500 vibratory stimuli delivered with a fixed ISI of 1s and there was a minimum of 2 minutes between each run. The order of presentation of each block was randomised for each subject and the stimuli consisted of 70Hz sine wave vibratory bursts of 20ms, 50ms, 70ms, 150ms, 170ms, or 250ms.

The stimuli were delivered only to the right hand in order to minimize the length of the recording session.

5.3.1.2 Experiment 4

In this experiment a total of six trial runs were performed, two of which utilised the same protocol as described above in experiment one, but used a 1000ms stimulus duration. The other four were attended trials in which the subject was asked to fixate on a dot in front of them and to count the number of deviant stimuli (a clearly detectable change in duration). Instead of a video, white noise was administered through head phones to mask any sound from the oscillator. Stimulus durations of 20ms, 70ms, 150ms and 250ms were used in these attended trials and each block was presented in a random order and counter-balanced.

5.3.2 Experiment 5 – Intracranial case study

The recording session lasted 1 hour and was performed on the telemetry ward, with the patient sitting up in bed watching a self – chosen video on a wall-mounted screen 3 meters away. A vacuum cast was not used as the subject had intravenous lines insitu, instead pillows supported the hand and wrist and the subject was monitored to ensure that only these fingers rested on the T-bar and that there was minimal joint movement. The stimuli were constructed and delivered in the same fashion as described in section 4.3.3.2 save that the impedance head was not used as the force processing equipment could not be taken to the ward. The stimuli were delivered to the right hand, which was contra-lateral to the hemisphere on which the SEAs were implanted. As in experiment 3, the subject was instructed to ignore the stimuli but for the sake of brevity, only the 20ms, 250ms and 1000ms stimulus durations were presented.

Intracranial recordings were collected from most subdural contacts. However recordings could not be obtained from G001, and G002, owing to an excess of 50Hz interference. The reference and ground were placed at SA02 and

SA01 respectively (fig. 5.1). Recordings were obtained using the Neuroscan recording system as described in section 4.3.3.4 with the only variation being that the sampling rate was increased to 1000Hz. The continuous data was analysed further offline.

5.3.3 Offline analysis

In each study the data was re-montaged using a global field power reference (section 4.3.4) in order to minimize the possible effects of the acquisition reference and an ocular correction algorithm was applied (Neuroscan, 4.2).

In experiment 3, epochs of -50 to 600ms were constructed using Neuroscan 4.2 software. The epochs were baseline corrected using the average voltage calculated between -50ms and -10ms pre-stimulus and digitally filtered between 1 and 50Hz with a 12-dB/oct slope. Automatic artefact rejection of +/- 75μV was performed based on all channels then the epochs were averaged. For each subject two averages were obtained and compared to ensure replicability before inclusion in the grand average.

In experiments 4 and 5, epochs of –50 to 1600ms (longer duration stimuli) and –50 to 600ms (attended condition stimuli) were similarly constructed as outlined above.

Only the P50, P100 and a later negative component, labelled No1, were analysed for all stimulus durations, as these were most likely to reflect the onset and offset of the stimulus, with the P50/P100 complex being analogous to the visual CI/CII complex (section 5.1.1.1). However at the longer durations a small positive component, Po1, was observed preceding No1 and the values for this component were included in the analysis for the stimulus durations over 170ms. Amplitude and latency measurements were taken from electrodes P7, P8, C1, Cz,

C2, FC1, FCz and FC2. In experiments 3 and 4 analysis was performed using repeated-measures ANOVA with duration (20, 50, 70, 150, 170, and 250ms) and electrode (see above) as factors. Repeated measures ANOVA (duration x condition) was also performed to compare the mean amplitude and latencies recorded in the attended and unattended groups. Bonferroni analysis (Hsu, 1996) was performed posthoc.

5.4 Results

5.4.1 Experiment 3

The averaged evoked potentials consisted of a sequence of peaks, N35-P50-N70-P100-N140-N200-Po1-No1 and were recorded between the fronto-central and left parietal regions, with phase reversal over the centro-parietal area (fig. 5.2A).

The latencies of the P50 and P100 components showed no significant difference between the different stimulus durations (fig. 5.3A). However the P50 component showed a significant difference between electrode locations ($F(5, 40)=51.79$ $p<0.001$) with an increase in latency over the right scalp electrodes (ipsilateral to the side of stimulation). There was no significant difference in the P100 latency between electrode locations.

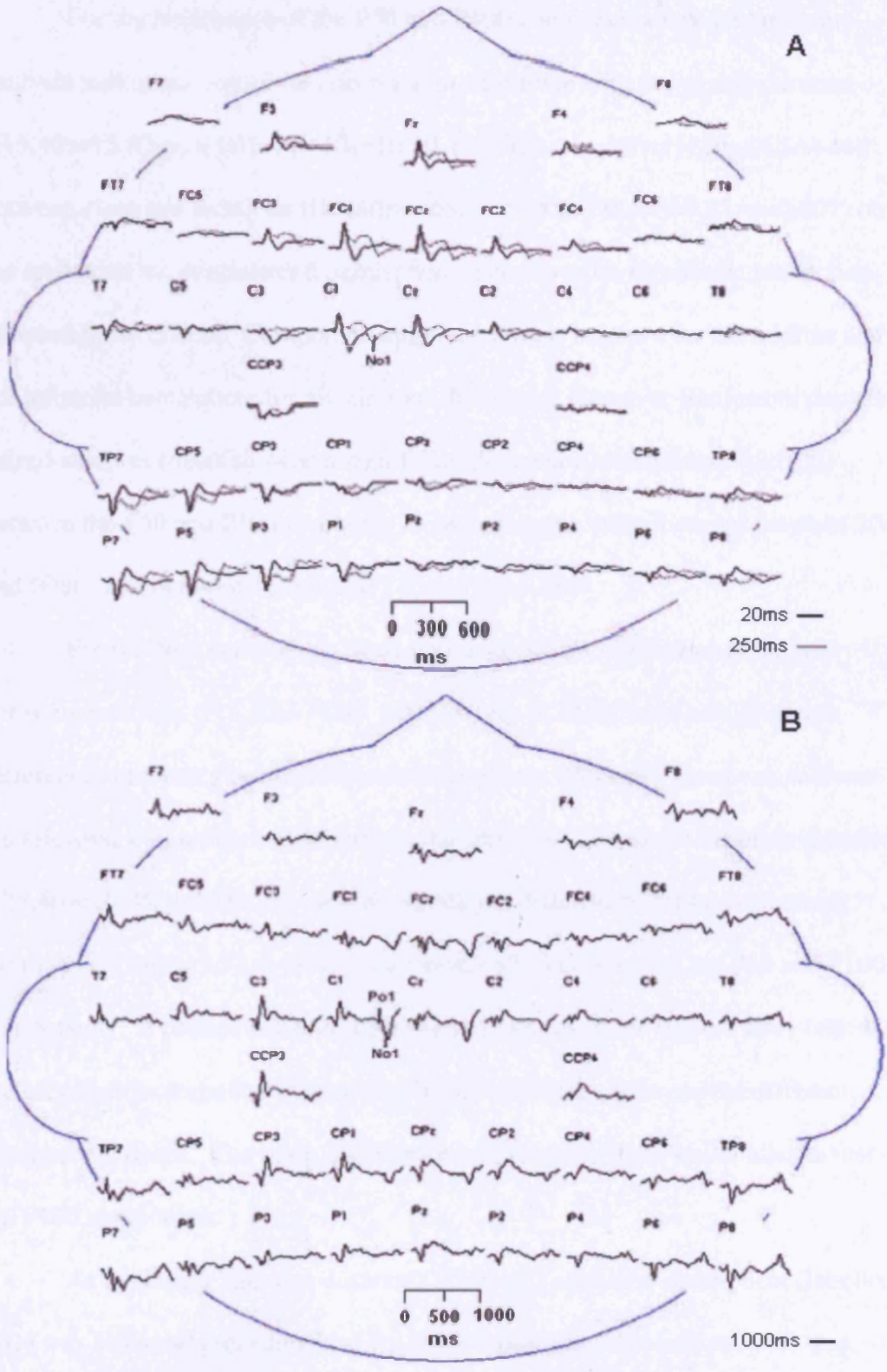


Figure 5.2: A Schematic of the scalp distribution of the grand average responses (A) Results from experiment 1, with the 20-ms and 250-ms duration responses overlaid. (B) Results from experiment 2, 1000-ms stimulus duration responses. There is clear lateralization of both the sustained potential and *on-off* responses.

For the amplitudes of the P50 and P100 components repeated measure analysis indicates a significant decrease in amplitude with increasing duration ($F(5,40)=15.80$ $p< 0.001$; $F(5,40)=10.29$, $p<0.001$ respectively) (fig. 4.3A) and between electrode locations ($F(5,40)=9.68$, $p< 0.001$; $F(5,40)=9.57$, $p<0.001$) on the ipsilateral vs. contralateral hemisphere. There was no significant interaction between these effects. Component amplitudes were largest over the midline and contralateral hemisphere for all stimulus durations. However Bonferroni corrected paired-samples *t*-tests showed a significant difference in amplitude ($p<0.05$) between the P50 and P100 responses to each duration stimuli except between 20ms and 50ms, and between 150ms and 170ms (fig. 5.3B).

For the No1 component, there was a significant difference in latency between durations ($F(5,40)=74.63$, $p<0.001$; fig. 5.3A&C) but no significant differences in latency between electrode locations. Repeated measures analysis also showed a significant difference in the amplitude across the different durations ($F(5,40)=16.94$, $p<0.001$) as well as significant differences between electrode locations ($F(5,40)=5.32$, $p<0.01$) in a manner similar to that of the P50 and P100 components. It peaked between 120-144ms (average =129.7ms ±9.1ms) following the offset of the stimulus, with no significant difference between the different stimulus durations. The scalp distribution of this component was similar to that of the P100 component.

At the longer stimulus durations (150ms+) a positive component (labelled Po1) was observed preceding No1 by 85ms ±4ms, but in several subjects was obscured by other waveform components. At the shorter durations this component was not readily observable, most likely being subsumed by the P100 or N140 components.

Also at the longer durations, the waveform did not reach the baseline between the end of the P100/N140 components and the start of the Po1/No1 complex, rather there was a negative baseline shift that lasted throughout the duration of the stimulus. This phenomenon appeared maximally over the left centro-parietal region (Fig 5.2B). The presence of a similar shift in the responses to the shorter durations is suggested by the broadening of the P50/P100 complex observed when comparing the responses to 20ms, 50ms and 70ms stimulus durations (Fig.5.3A). This may reflect a sustained potential similar to that reported in the auditory and visual systems (section 5.1.1).

In order to examine the possible effects of habituation or anticipation on the resulting waveforms the grand average responses to the first and one hundredth stimuli were compared. There was no difference in the morphology or distribution of the responses. However *t*-tests comparing the amplitudes of the P50, P100 and No1 components showed them to be significantly higher for the first stimulus (P50: $t=-3.44$, $p<0.01$; P100: $t=-3.31$, $p<0.01$; No1: $t=-2.51$, $p<0.05$), which was to be expected when taking into account the effects of habituation (section 2.1.2.1). Additionally, there was a clear P300 component present in the first response that was not present in the later response. When the grand average response to the one-hundredth stimulus was compared to that of the one hundred and fiftieth there was no significant difference in latency, amplitude, scalp distribution or morphology.

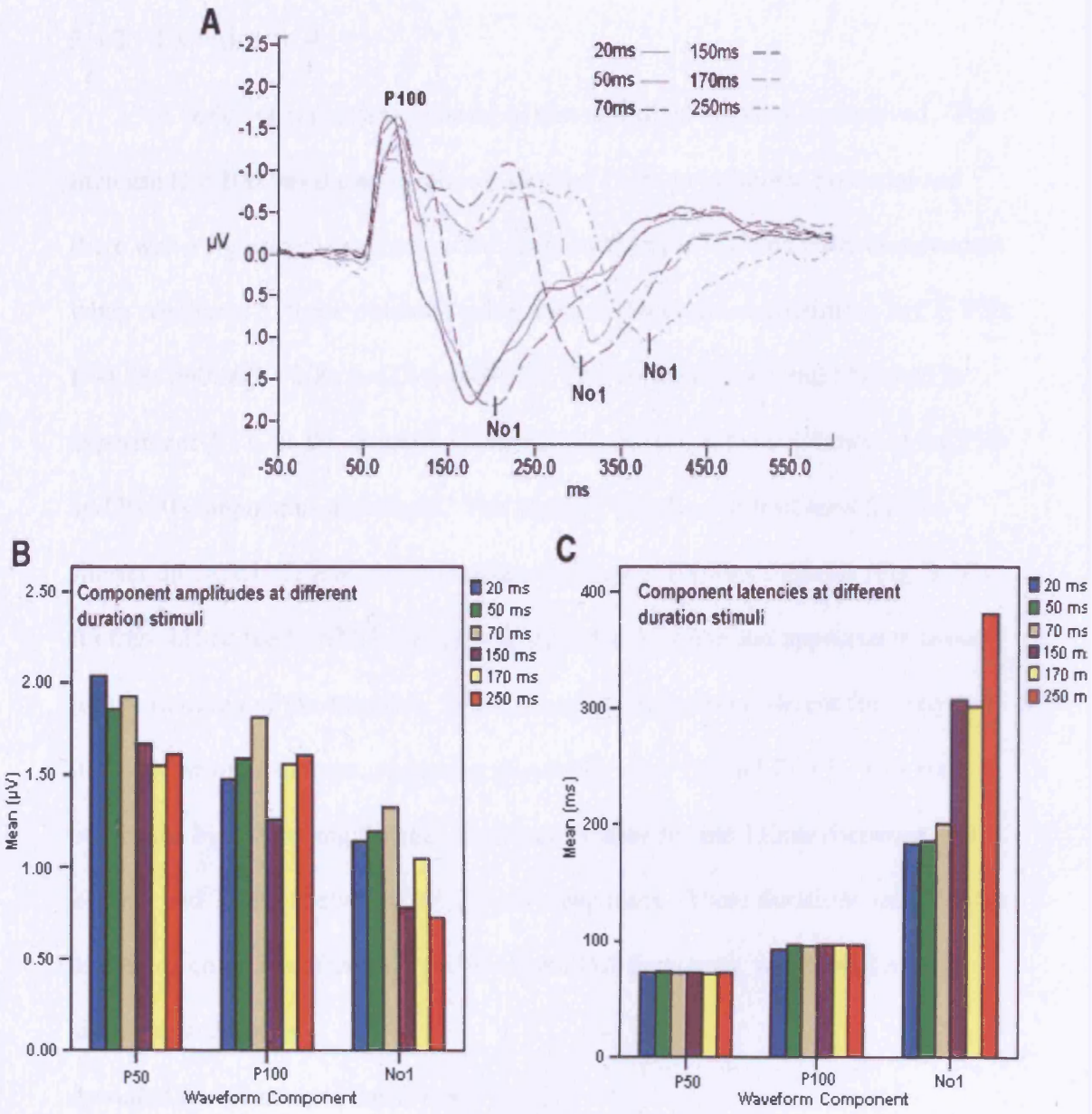


Figure 5.3: Study 1. (A) Different stimulus durations at C1 (No1 and P100 are phase reversed at C1). Note the increase in latency of the No1 component. (B) The difference between the component amplitudes with different duration stimuli. (C) The difference between the component latencies with different duration stimuli.

5.4.2 Experiment 4

A series of waveforms similar to that described above was observed. The increase to a 1000ms duration stimuli showed a clearer sustained potential and there was a significant decrease in the amplitude of the P50 and P100 components when compared to those obtained using a 20ms duration in experiment 3 (C1: P50: t=-4.08; p=0.003; P100: t=-2.61, p=0.02). This followed the trend observed in experiment 3, i.e. as the duration of the stimuli increased the amplitude of the P50 and P100 components decreased. The negative baseline shift observed at the shorter durations became more prominent using the 1000ms stimulus (Fig. 5.2B). It often shifted the Po1/No2 complex negative to baseline and appeared to persist for the duration of the stimulus. It had a scalp distribution different from the transient *on-off* responses, appearing maximally over C3 and CCP3. This was confirmed by comparing the maximum area values for the 170ms (between 160-270ms) and 250ms (between 160-366ms) responses. These durations were chosen as they discount the effects of the N140 and Po1 responses, which tend to have similar distributions.

Attended vs. unattended conditions:

The results obtained from the runs in which the subject had to attend the stimuli show a similar waveform morphology to those previously described with the addition of a clear N250/P300 complex in response to the target stimuli. In general, the responses obtained in the attended condition appear slightly earlier and higher in amplitude (fig. 5.4). However the decrease in latency was only significant for the P50 and P100 components (C1: P50, $F(1,3)=13.54$, $p<0.05$; P100: $F(1,3)=15.34$, $p<0.05$). There was a significant increase in the amplitude of the P50, P100, N140 and No1 components (C1: P50, $F(1,3)=68.12$, $p<0.01$; P100:

F(1,3)=45.54, p<0.01; N140: F(1,3)=168.50, p<0.001; No1: F(1,3)=37.67, p<0.01). The N140 amplitude enhancement was particularly notable in the responses obtained using 170ms and 250ms (Fig. 5.4).

Area measurements were made between 150 and 250ms in order to compare changes in the sustained potentials and this time window was chosen in order to minimize the contribution from the N140 and No1 components. T-tests comparing the area values in the attended and ignore conditions for the 170ms and 250ms durations showed a significant increase in the attended condition (170ms: t=2.67, p<0.05; 250ms: t=3.28, p<0.01); suggesting there was also an increase in the amplitude of the sustained response with attention.

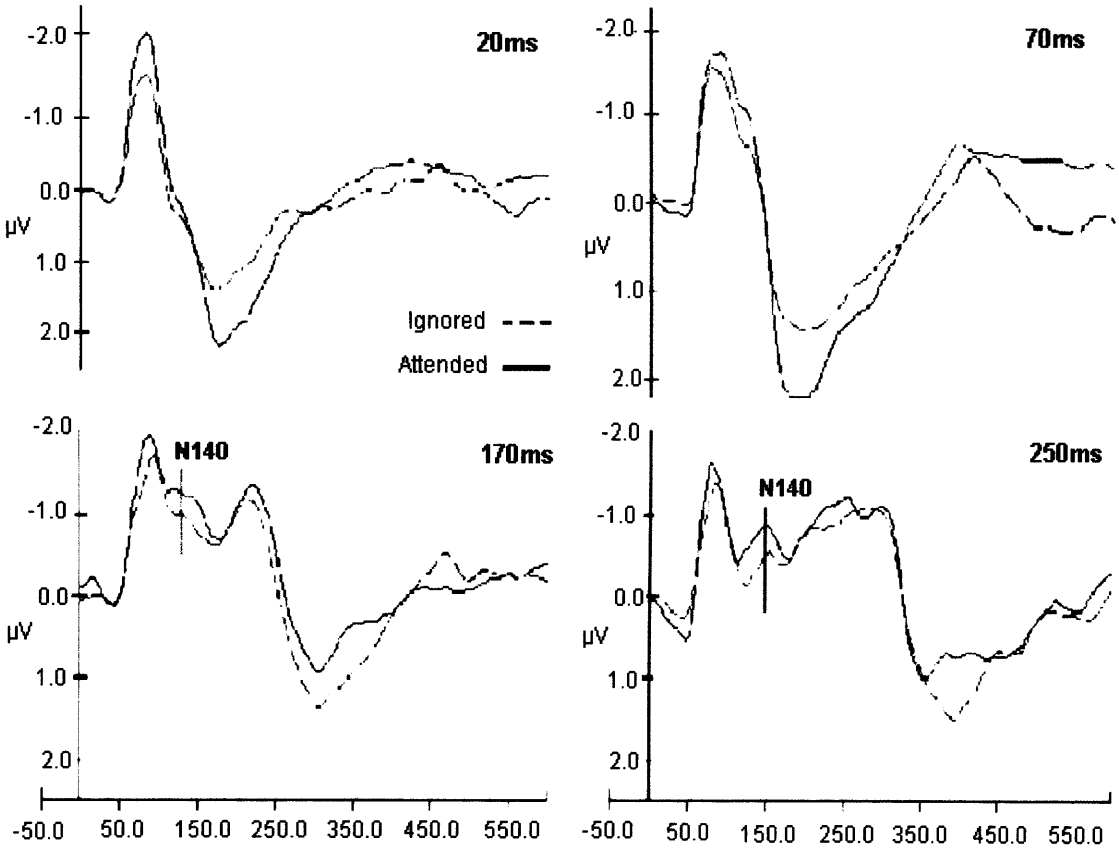


Figure 5.4: Comparison of attended and ignored SSEP responses to nontarget stimuli at C1. Note the enhancement of the N140 component.

5.4.3 Experiment 5 – Intracranial recording

The ERP waveforms recorded from the subdural grid may be seen in fig. 5.5. They consisted of a small negative deflection at 46-54ms followed by a large positive deflection at 75-80ms; these appeared to phase reverse over the post-central sulcus. This was immediately followed by a large negative component, probably analogous to the scalp N200, which appears to increase slightly in latency as the duration of the stimulus increased. At a stimulus duration of 20ms the latency was 148ms, at 250ms it was 164ms and at 1000ms it was 175ms. A similar component was seen from the scalp recordings, but was not as well defined. A negatively shifted sustained component was then seen, recorded from the contacts straddling the post-central gyrus. This component was most clearly seen using the 1000ms stimulus. No shift was readily apparent when using the 20ms stimulus. Following this shift at 250 and 1000ms stimulus durations was a small negative deflection followed by a large positive deflection which was most notable over the superior part of the grid, on the contacts covering the rostral section of the post-central gyrus.

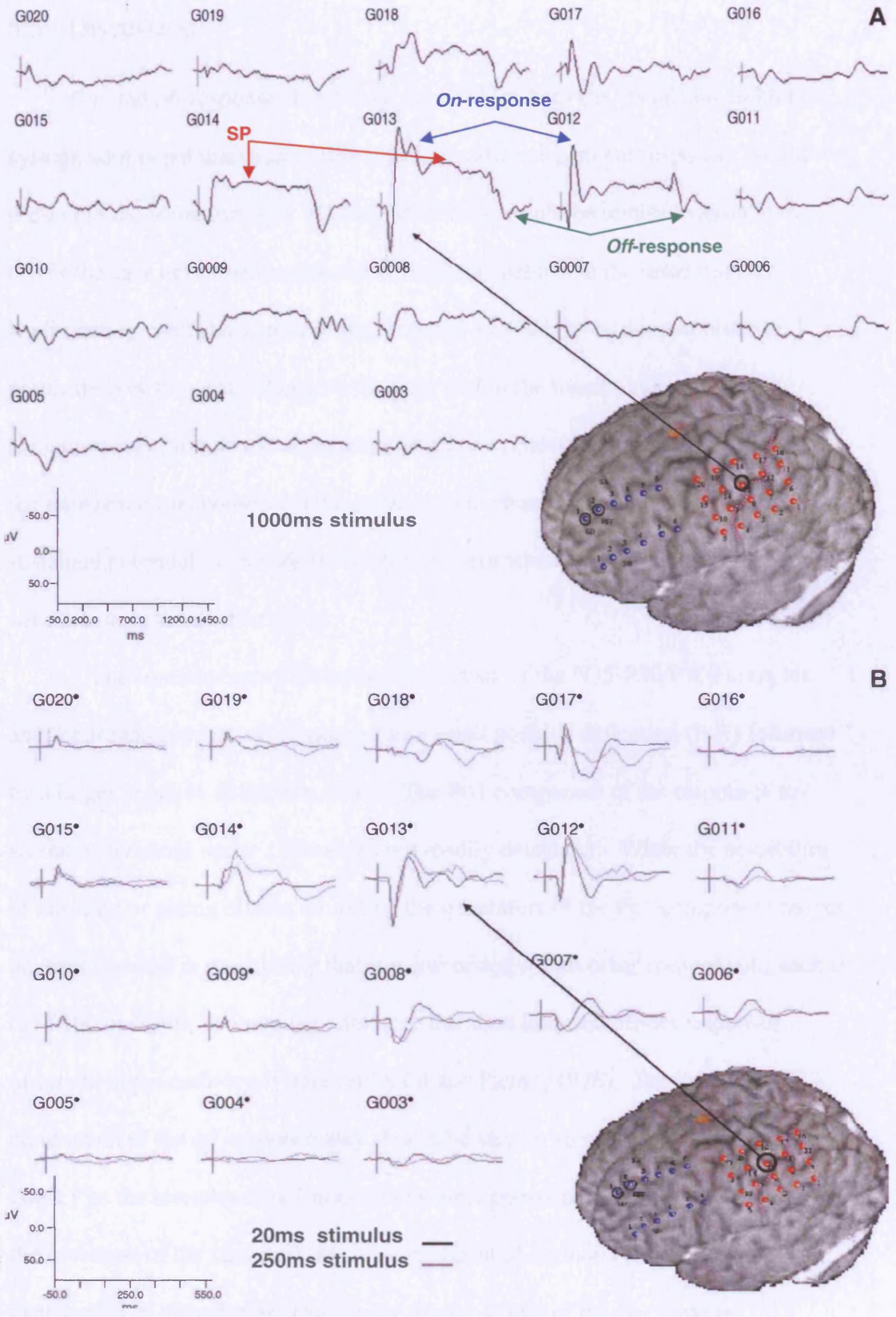


Figure 5.5: Experiment 3. (A) 1000ms vibratory somatosensory responses. (B) 20ms and 250ms vibratory somatosensory responses. The sustained potential (SP) has a more anterior distribution than the *on* and *off* responses.

5.5 Discussion

On- and *off*-responses have been reported for both the visual and auditory system, so it is not unexpected that similar duration dependent responses would be present in the somatosensory system; however it would be remiss to assume that this is the case or to assume that these responses behave in the same manner. Rudimentary characterization of these responses needs to be done in order to predicate how they may change or interact within the manipulation of somatosensory stimuli and subsequent cognitive processing. This study examines the transient *on*-response, and the previously uncharacterised *off-* response and sustained potential, in the somatosensory system when using mechanical stimulation of the median nerve.

The somatosensory *on*-response consists of the N35-P50/P100 complex and the somatosensory *off*-response has a small positive deflection (Po1) followed by a larger negative deflection (No1). The Po1 component of the responses to stimulus durations under 150ms was not readily detectable. While the possibility of masking or gating effects inhibiting the generators of the Po1 component cannot be discounted, it is most likely that it is imbedded within other components, such as the P100 or N140, in a manner similar to the short duration off-set responses observed in the auditory system (Hillyard and Picton, 1978). The later No1 component of the *off*-response may clearly be seen to significantly increase in latency as the stimulus duration increases, but appears an average of 130ms after the cessation of the stimulus; this is independent of stimulus duration. The distribution of the *off-* response is very similar to that of the *on-* response, appearing maximally over the contra-lateral parietal region, with phase reversal over the central-parietal areas.

Also seen was a significant decrease in the amplitude of the P50/P100 components with increasing stimulus duration but there was no significant change in the No1 amplitude. A similar phenomenon in the auditory system was reported by Hillyard and Picton (1978) who found that as tone bursts were made longer but onset asynchrony was fixed, then the N1/P2 onset response became smaller and the N1/P1 offset response became larger. This interaction between the two responses indicates that they are not physiologically independent processes. More recent work has shown that the N1 and P1 *on*- and *off*-components are generated in overlapping cortical regions and the auditory 'off' response is generated primarily by a group of neurons that are topographically near, but slightly more anterior, to those generating the 'on' response. However these differences are very small and in some cases do not reach significance (Noda et al., 1998; Pantev et al., 1996). In the somatosensory system, cellular recordings have found rapidly adapting neuronal populations that respond either to the onset or offset of a stimulus or to both (Sur et al., 1984). Taken together this evidence suggests that the somatosensory transient onset and offset responses may also have separate generators and that the similar scalp distribution of the *on*- and *off*- responses seen in this study does not preclude the possibility of separate, but closely adjoining neuronal populations.

The 70Hz vibratory stimulus used in this study preferentially stimulates the Pacinian corpuscles which project bilaterally to the SII area of the somatosensory cortex (Ferrington and Rowe, 1980; Maldjian et al., 1999) and SERPs recorded from the scalp show a larger, more distinct P100 response than is seen with other forms of mechanical stimulation (Hämäläinen et al., 1990), which is one of the advantages of using this type of stimulation. In this study the *on*-response is a

complex of the P50 and P100 components, often with a more pronounced P100. These components are thought to arise from SI and SII cortices respectively (Hämäläinen et al., 1990) and it is possible, even probable, that the *off*-response we recorded is similarly a complex of components reflecting activation of different cortical areas. The contra-lateral emphasis of these responses seen in this study may reflect the contribution of the lateralized P50 (SI) responses and more precise stimulation may be able to separate the P50 and P100 responses and there may even be a difference between SI and SII *on*- and *off* -responses. Further study may reveal similar processes taking place in higher order somatosensory areas such as Brodmann area 40 (Section 1.2.3.1).

Also observed was a *sustained*-potential following the P100 component where the waveform approaches but does not come back down to baseline before the *off*-response appears. This is similar to the *sustained*-field response to long duration stimuli reported in the auditory and visual systems (Crevits et al., 1982; Hari et al., 1997; Picton et al., 1978b). In the auditory system this potential has been shown to be distinct from the CNV (Picton et al., 1978b) and is seen using stimulus durations over 500ms (Section 5.1.1.2). It had a distribution different from that of the *on*- and *off*- responses, being more lateral and anterior, but still showed a clear emphasis over the hemisphere contralateral to the side of stimulation. As this distribution is different from the P50 and P100 components it is possible that the cortical generators may arise in an area separate from the SI or SII regions. Cellular recordings in area 3b of owl and macaque monkeys have found a group of slowly adapting neurons that respond not only to the onset and offset of a stimulus, but also respond throughout the duration of the stimulus. These are located only in the middle layers of the cortex, with a slightly different

distribution from those cells responding only to the onset or offset of the stimulus (Sur et al., 1984). This *sustained*-field is most clearly seen at the longest stimulus durations used, 170ms, 250ms and 1000ms for both the intracranial and scalp recordings. The onset of this potential at the scalp is between 130-165ms, which is comparable to the 120-180ms onset reported for the auditory sustained potential (Pantev et al., 1996; Picton et al., 1978b) and considerably earlier than the latencies reported for the CNV (>400ms) (Rebert and Knott, 1970). It was recorded in both the attended and unattended experimental conditions, which also makes it unlikely to be the CNV.

Attention to the somatosensory stimuli can enhance the amplitude of the scalp recorded transient and sustained responses. In the task given attention was required throughout the duration of the stimuli in order to discriminate changes in the stimulus duration. The increase in the amplitude of the sustained response under these conditions may reflect an actual increase in the sensory *sustained* – potential, but the possibility of an added CNV associated with temporal uncertainty can't be ruled out. The increase in amplitude and decrease in latency of the transient *on*- and *off* –responses are similar to those reported for other sensory modalities.

5.6 Conclusions

It is early to comment on the clinical or prognostic value of these findings, but it is likely that pathologies affecting the somatosensory system will disrupt these components. The characterization of the normal *on*- and *off*-responses will allow for the identification of abnormalities in the somatosensory. This may aid in diagnosing and characterizing certain disease processes.

The similarity between the late evoked potential responses in the primary sensory cortices may reflect a common process that enables further cognitive processing and sensory integration. Further study examining other parameters, such as varying the ISI, frequency or intensity of the stimulus, would help to characterize these responses. This would lead to a more thorough understanding of how the somatosensory responses are similar, and different, to those of the other modalities; providing the necessary foundation in understanding how different sensory information is integrated and how the differing temporal development of these sensory responses may underlie some of the cognitive changes that are seen in human development.

Subsequent experiments in this thesis use and compare SERP responses to different duration vibrotactile stimuli. Thus it was important to characterize the SERP responses to different duration stimuli so that the effects of duration could be predicted and controlled for.

Chapter 6: Effects of stimulus frequency and duration on somatosensory discrimination responses.

6.1 Introduction

A discrimination response to an infrequent change in a stream of continuous, repetitive stimuli may be recorded as an ERP component, the mismatch negativity (section 3.1). It is thought to be generated by a difference between the sensory input of a deviant stimulus and the neural representation of the physical features of the preceding repetitive standard stimuli. A number of studies have reported a somatosensory mismatch response (sMMR) but there are inconsistencies between them regarding the latency and morphology of the response (for discussion see section 3.4.1).

6.1.1 Aims of this study

The following experiments record SERPs using an oddball paradigm that presented changes in either the duration or frequency of a vibratory stimulus. The objective was to further elucidate the characteristics of the SERPs related to pre-attentive discrimination, to expand on the previous work, and offer an explanation for some of the inconsistencies reported in the previously published data.

6.2 Subjects

A different group of subjects participated in each experiment (experiment 6: N=12, 18-38yrs; experiment 7: N=10, 19-34yrs) and all were right handed.

6.3 Methods

6.3.1 Stimuli

Section 4.3.3.2 describes the methods for stimulus construction and delivery.

In experiment 6, paired stimulus durations of 20/70ms, 50/150ms, and 170/250ms were present as one of six conditions. In experiment 7, the stimulus duration remained constant at 20ms, but two different frequencies were used, 70Hz and 200Hz and these were presented as one of two conditions.

Expt	Condition	Standard	Deviant
1	1	20ms	70ms
	2	70ms	20ms
	3	50ms	150ms
	4	150ms	50ms
	5	170ms	250ms
	6	250ms	170ms
2	1	70Hz	200Hz
	2	200Hz	70Hz

Table 6.1 *Stimulus conditions used in experiments 1&2.* In experiment 1 the frequency was kept constant at 70Hz. In experiment 2 the duration was kept constant at 20ms.

These frequencies were chosen to specifically target the Pacinian system and avoid complications, which may arise from different cortical representations of the Pacinian and non-Pacinian systems (section 2.2.3).

6.3.2 Experimental procedure

Section 4.3.3.3 describes the general experimental setup.

The subjects were tested in a single recording session lasting 2hrs with a 10minute break in the middle. In both experiments the stimulus was presented

with an ISI of 1000ms and a standard probability of 90% and a deviant probability of 10%.

6.3.2.1 Experiment 6

In experiment 6, subjects were randomly presented with 12 blocks, each consisting of 500 vibratory stimuli, with a minimum of 2 minutes between blocks. Each block consisted of one of the 6 conditions and each condition was presented twice to the right hand. Two blocks each of condition 1 and 2 were delivered to the left hand. Testing of the left hand was limited to only the 20/70ms pairs owing to time constraints.

Of the 12 subjects participating in experiment 6, 8 were also presented with two control trials in which the 20/70ms and 170/250ms pairs were presented with equiprobability.

6.3.2.2 Experiment 7

In experiment 7, both hands were tested, each in turn being randomly presented with 4 blocks of 500 vibratory stimuli, again with a minimum of 2 minutes between blocks. Each block consisted of either of the two conditions with each condition being presented twice.

6.3.3 Continuous EEG recording

The electrode placement and method of recording the continuous EEG are described in section 4.3.3.4.

6.3.4 Discrimination Task

After testing, 15 of the 22 subjects taking part in the two experiments performed an active discrimination task in which they had to attend the stimuli and discriminate between the paired stimuli used in the previous experiments with the

addition of control pairs in which the two stimuli were the same. The stimuli were applied to digits 2 & 3 of the right hand via the T-bar apparatus used previously. Then, with the left hand, the subject pressed one button if the stimuli were the same and a different button if they were different. The buttons were clearly labeled to avoid confusion. During this task the sound of the stimulator was masked by white noise delivered via headphones. This prevented the use of auditory cues in discriminating between the stimuli. The stimulus pairs were presented in random order, 1 per second, and each pair occurred 5 times.

6.3.5 Offline analysis

Remontaging and epoch construction was performed as described in section 4.3.4. Then the averaged epochs for the pre-deviant standard and deviant stimuli were obtained for each block. The pre-deviant standard and deviant responses of the same duration or frequency were compared and a subtraction waveform obtained. Peak amplitudes and latencies for the main components were identified in the responses to the pre-deviant standard and deviant stimuli and the corresponding difference waveforms.

6.4 Statistical analysis

6.4.1 Scalp recordings

Repeated-measures analysis of variance (ANOVA) was applied with stimulus (deviant, standard), electrode (21 electrodes), duration (20, 50, 70, 150, 170, 250ms) or frequency (70Hz, 200Hz), and hand (left, right) as factors. The amplitudes of the subtraction waveform were normalized according to a scaling procedure outlined by McCarthy and Wood (1985) in order to evaluate differences between the scalp distribution of the left and right hands and between stimuli. The

Greenhouse-Geisser correction was used for the F values when the degrees of freedom were greater than 1 and the probabilities adjusted with the correction coefficient ε as necessary; the original degrees of freedom are presented for each analysis.

6.4.2 Discrimination task

The non-parametric data obtained in the discrimination task was analyzed using Cochrane's Q and McNemar tests.

6.5 Results

6.5.1 Scalp recordings

6.5.1.1 Distribution

A clear negative shift in the ERP responses to the deviant stimuli (labelled MN1) was observed between 100-200ms following stimulus onset (figs. 6.2 and 6.3). This was most marked over the central and fronto-central regions (for example see fig. 6.1).

ERPs were averaged across all deviants (frequency or duration) and the immediately preceding standards. Statistical analyses confirmed that the mean amplitude between 100-200ms of the deviant response was significantly higher than that of the corresponding standard response (*Experiment 6*: 70Hz stimuli: 20ms: $F(1,9)=6.64$, $p<0.01$; 50ms: $F(1,9)=6.027$, $p<0.02$; 70ms: $F(1,9)=10.56$, $p<0.002$; 150ms: $F(1,9)=5.96$, $p<0.03$; 170ms: $F(1,9)=5.22$, $p<0.04$; 250ms: $F(1,9)=5.35$, $p<0.04$. *Experiment 7*: 20ms stimuli: 70Hz: $F(1,9)=10.83$, $p<0.001$, 200Hz: $F(1,9)=10.44$, $p<0.002$.). A difference waveform was then obtained by taking the standard response from the corresponding deviant one. There was no

significant main effect in MN1 component amplitude between the different types of stimuli (frequency or duration) nor was there any difference in the amplitudes between the two hands. However there was a significant interaction effect between hand and electrode ($F(20,176)=3.63$, $p<0.001$, $\varepsilon =0.000$) owing to significantly higher amplitudes over the hemisphere contralateral to the side of stimulation (right hand stimulation: $F(1,168)=28.30$, $p<0.001$; left hand stimulation: $F(1,169)=15.38$, $p<0.001$).

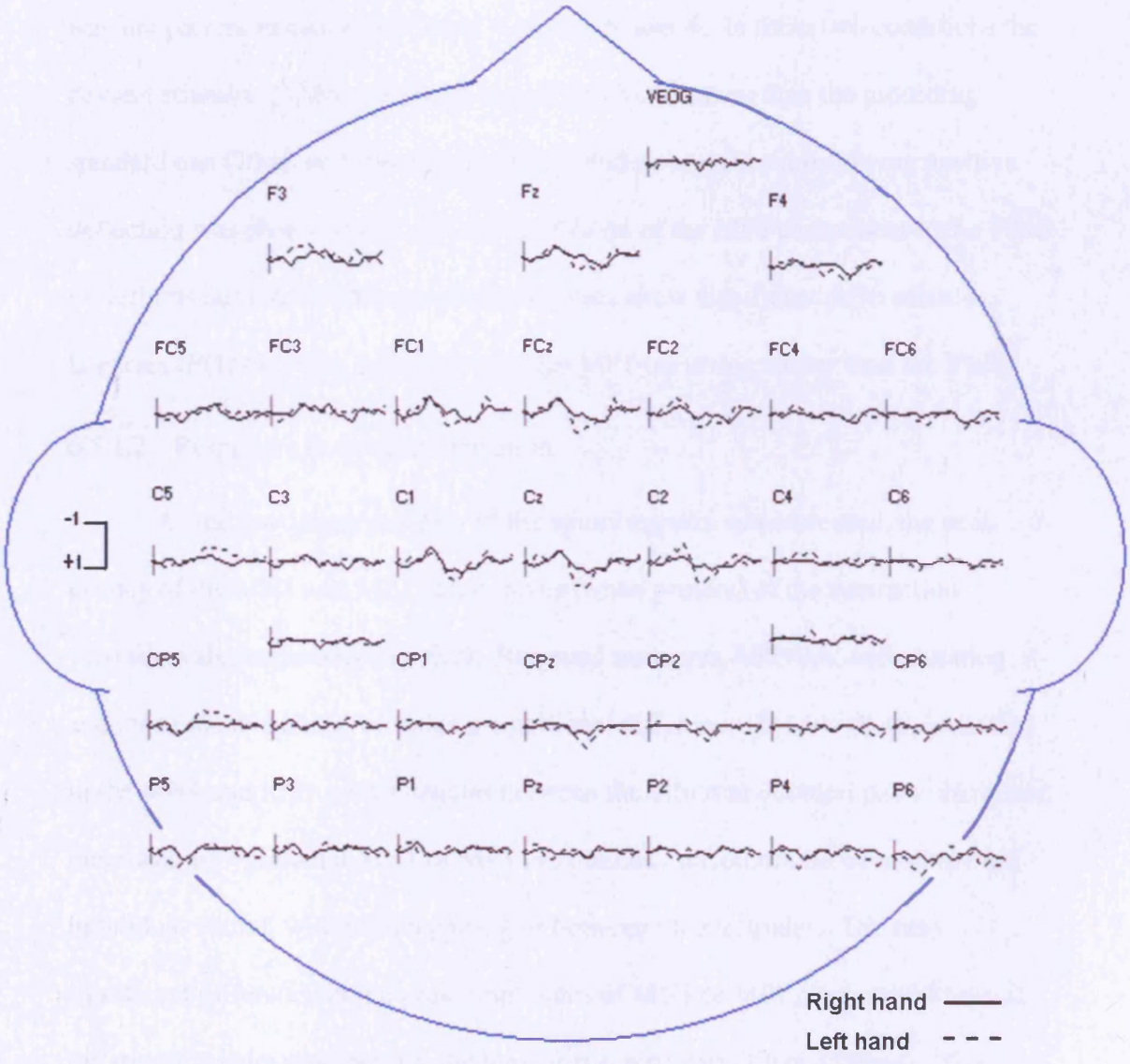


Figure 6.1: An example of the scalp distribution of the somatosensory mismatch response as a difference waveform obtained by subtracting the standard ERP from the deviant ERP; obtained using a 20ms/70Hz frequency deviant.

($F(4,9)=77.46$, $p<0.01$). However subtraction waveforms to this stimulus pair were only obtained in 5 out of the 12 subjects in experiment 6.

The 20ms/70ms stimulus pair was presented to both the right and left hands. There was no significant difference between the peak amplitudes or latencies of the MN1 component with regards to duration and hand. There was a significant latency effect of hand with no interaction with electrode ($F(1,9)=92.3$, $p<0.05$). The latencies from stimulation of the right hand tended to be shorter than that of the left.

6.5.1.3 Responses to frequency deviation

There was no significant difference between the peak latencies or amplitudes of the frequency MN1 or MP1 at either 70Hz or 200Hz. As seen with the duration MN1, there was a significant asymmetry in the amplitude between the electrodes, with responses over the hemisphere contralateral to the side of stimulation appearing higher in amplitude than those over the ipsilateral side ($F(1,9)=83.67$, $p<0.001$). While the frequency MN1 peak latency responses tended to be longer with left hand stimulation, this effect did not reach significance.

MP1 responses were clearly observed in both stimulus conditions and there was no significant difference in latency or amplitude between the two hands based on electrode position or stimulus frequency.

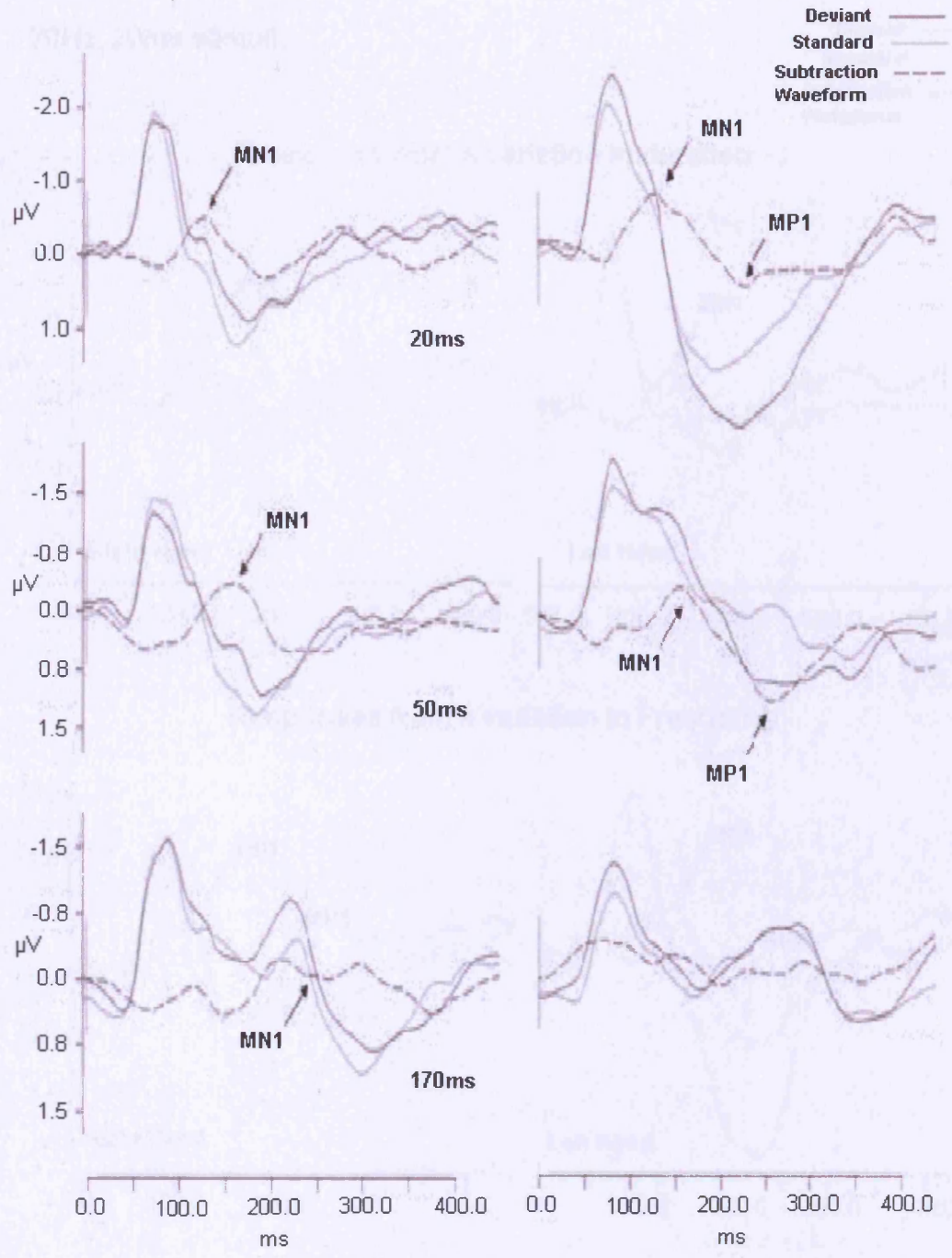


Figure 6.2: Experiment 6: Grand averaged responses at Cz to the deviant and pre-deviant standard stimuli at each of the stimulus durations tested. *Overlying* is the subtraction waveform. Note the lack of MP1 at 20 and 50ms stimulus durations. A very small or absent response at 250ms was observed in most of the subjects tested

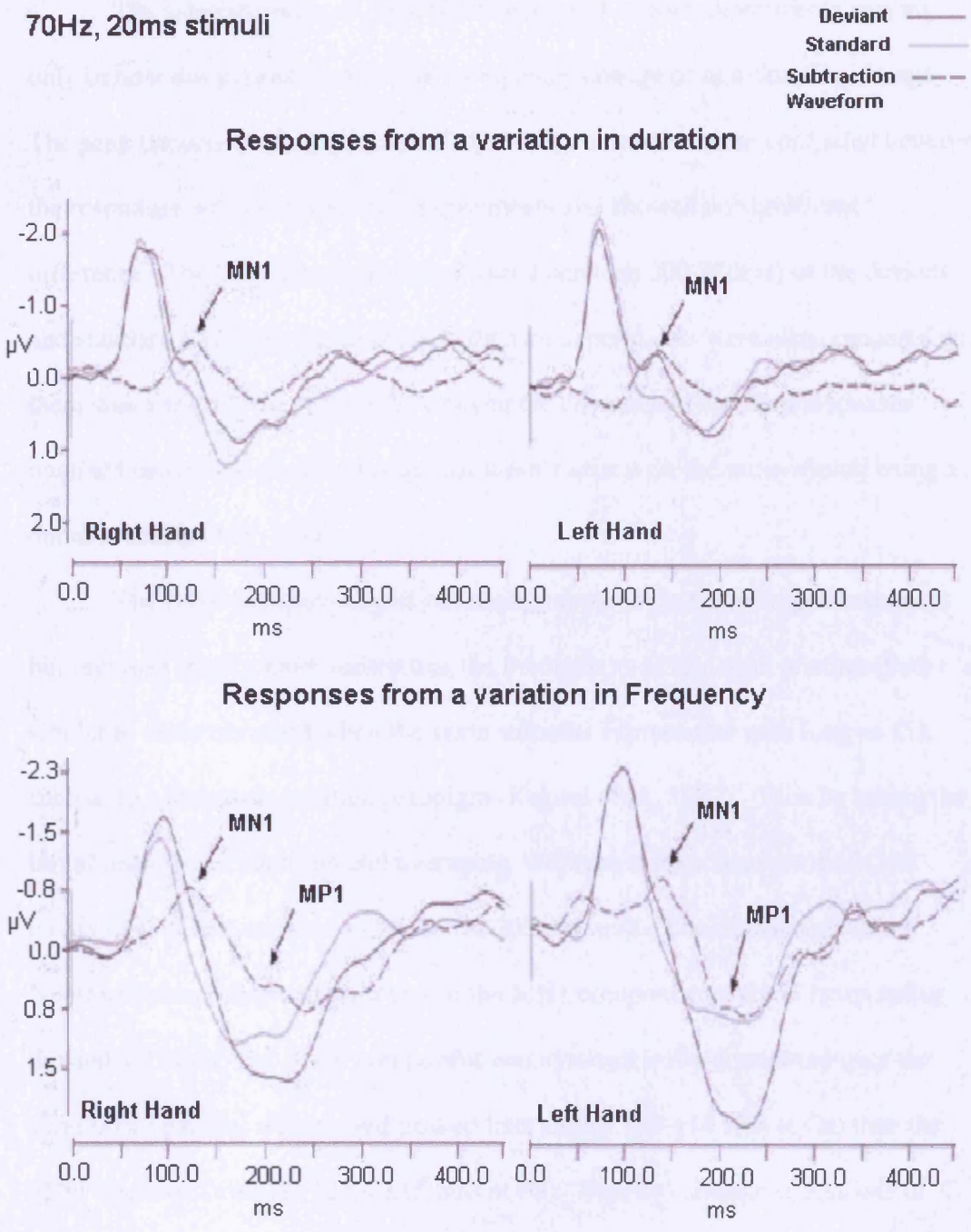


Figure 6.3: Grand averaged SERP responses at Cz for the same stimulus, 70Hz/20ms. The duration responses were obtained using an odd-ball paradigm in which the 20ms/70Hz deviant differed in duration from a 70ms/70Hz standard. The frequency responses were similarly obtained, but the 20ms/70Hz differed in frequency from a 20ms/200Hz standard. The duration responses lack the MP1 component.

The same stimulus of 20ms/70Hz was used in both experiments varying only in how it was presented, i.e. as a frequency change or as a duration change. The peak latencies and amplitudes of the MN1 component were compared between the responses obtained in the two experiments and showed no significant difference. The mean amplitudes (measured between 200-300ms) of the deviant and standard responses obtained from the two experiments were also compared and there was a significant difference between the deviant and standard responses obtained using a frequency change that wasn't seen with the same stimuli using a duration change (fig. 6.3).

The N140 component was not readily apparent in the averaged responses, but previous studies have shown that the first responses in a train of stimuli are similar to those obtained when the same stimulus is presented with long an ISI, such as in a standards-omitted paradigm (Kekoni et al., 1997). Thus by taking the initial response of each run and averaging, we were able to measure the N140 component of the response to the 20ms, 70Hz stimuli. The distribution of the N140 was then compared with that of the MN1 component of the corresponding deviant stimulus. The N140 component was symmetrically distributed over the central and parietal regions and peaked later (mean 160 ±14.5ms at Cz) than the MN1 response (average 125.4 ±15.5ms at Cz). Repeated measures analysis of variance (component x electrode location) of the mean amplitude between 100-200ms showed a significant component by electrode interaction ($F(6,42)=3.56$, $p<0.001$, $\varepsilon=0.001$) and this was due to differences over the central ($F(1, 9)=3.55$, $p<0.01$) and parietal ($F(1,9)=3.14$, $p<0.05$) electrodes. The N140 component showed no difference in amplitude across C3-C4 ($t(9) = 1.05$, not significant) or P3-P4 ($t(9) = -0.635$, not significant). However the MN1 component did show a

significant difference in amplitude between the electrode pairs C3-C4 ($t(9) = 3.48$, $p<0.01$) and P3-P4 ($t(9) = -2.43$, $p<0.05$).

In addition to the N140, a clear, broadly distributed P300 response was also observed in the first responses (peak latency average = 296.8 ± 30.2ms at Cz) similar to the novel P300 reported by Yamaguchi and Knight (1991). It appeared later than the MP1 component (peak latency average = 196.5 ±28.8ms at Cz) and was more widely distributed (fig. 6.4). Peak latency and amplitude measurements at Cz for each stimulus condition used in experiments 6 and 7 are shown in appendix 7.

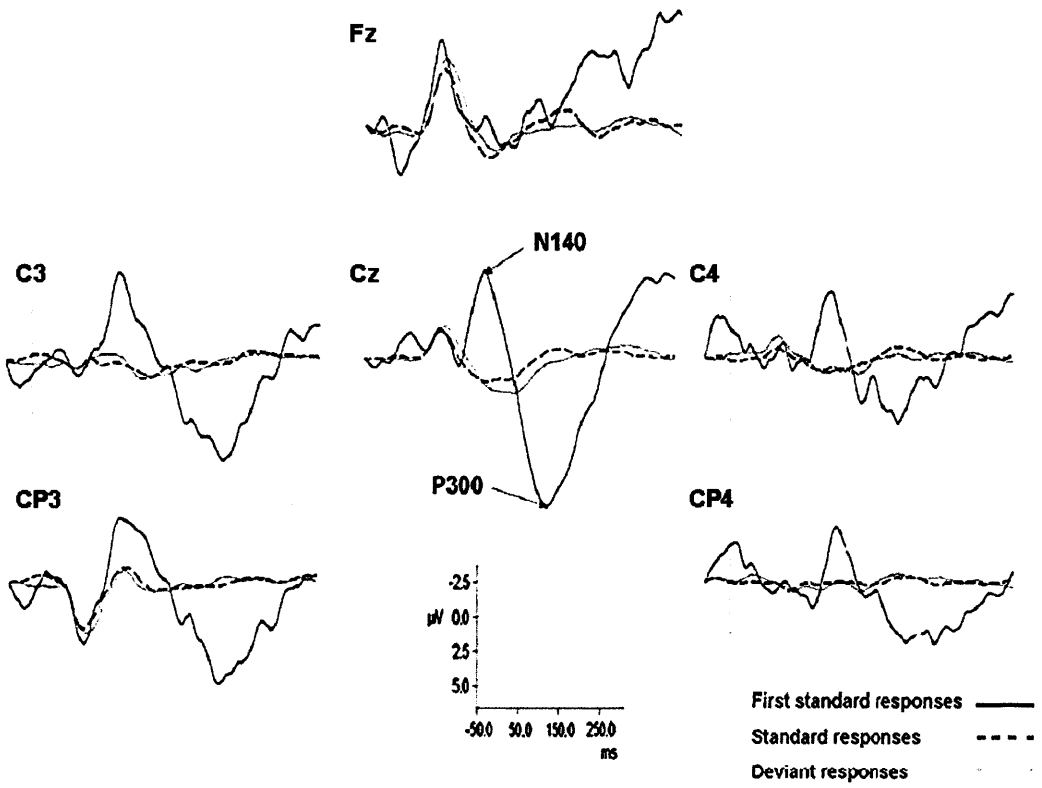


Figure 6.4 Grand average of the first response and the corresponding first deviant response to 70Hz/20ms stimuli. A large N140 and P300 component are observed in the first standard responses. These are not clearly seen in the averaged standard responses.

6.5.2 Discrimination task

The results are displayed in appendix 7. The subjects were able to successfully discriminate differences between the stimuli presented 78-98% of the time in most cases with no significant differences in success rate between the stimulus pairs. However when presented with the 250_170ms and 170_250ms stimulus pairs successful discrimination was only seen 19-22% of the time, thus showing a significant difference from the results obtained for the other stimuli pairs (Cochrane's Q = 503.827, p<0.001) (fig. 6.5).

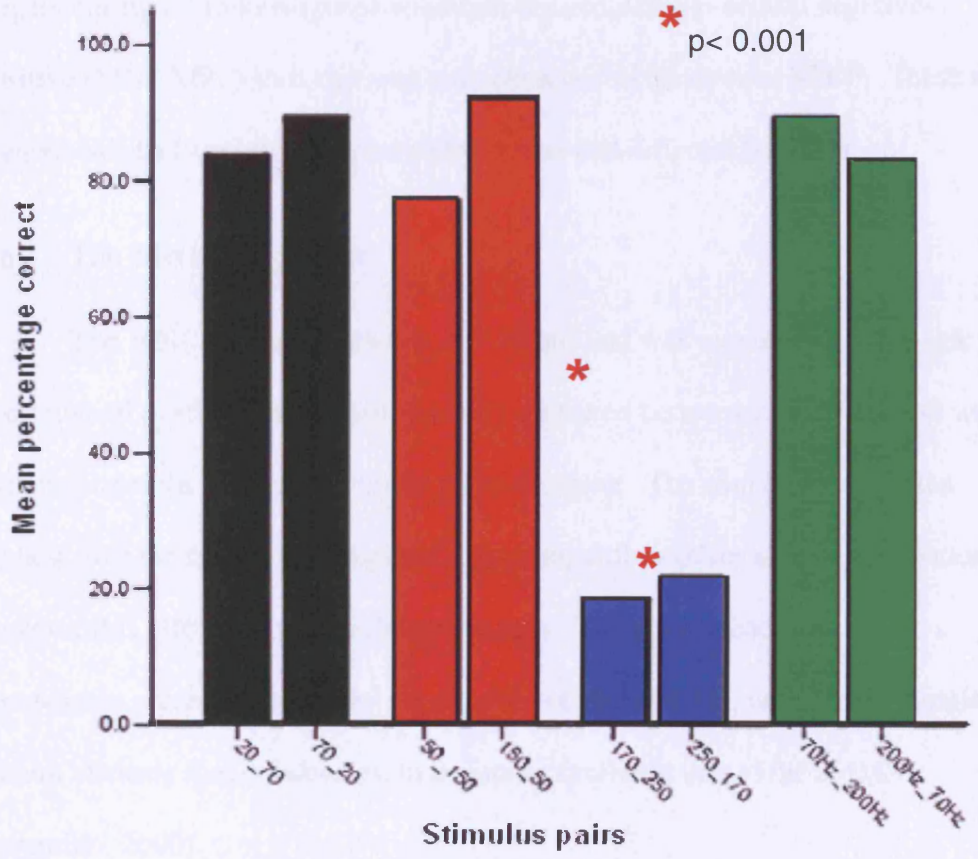


Figure 6.5: Results of the discrimination task. Subjects were significantly worse at discriminating between the 170 and 250ms duration pairs (blue) regardless of the order in which the two durations were presented (p<0.001).

There was a second trend observed in which stimulus conditions that presented the shorter stimuli first showed a tendency for more errors in discrimination than in the counter condition where the longer stimuli was presented first. However this was only significant between the 50_150ms and 150_50ms pairs (McNemar test; p=0.002)

6.6 Discussion

In the present study a change in either the duration or the frequency of vibratory stimuli presented in a pseudo-random sequence to the middle and index fingers during a stimulus-ignore condition elicited a fronto-central negative-positive (MN1-MP1) shift that was only observed in the deviant SERP. These two components had slightly different distributions and different latencies.

6.6.1 The MN1 component

The MN1 appeared between 100-200ms and was maximal over the side contralateral to stimulation while the MP1 appeared between 150-250ms and was maximal over the vertex and central parietal region. The amplitude was often highest over the right centro-parietal region, regardless of the side of stimulation; however this effect did not reach significance. The peak latencies of both components were influenced by the duration of the stimulus, with longer duration stimuli eliciting longer latencies, in a manner similar to that of the aMMN (Jaramillo, 2000).

Several studies report a clear fronto-central negative shift in response to an infrequent change in a stream of stimuli (Akatsuka et al., 2005; Kekoni et al., 1997; Kida et al., 2001; Shinozaki et al., 1998), but there have been clear discrepancies with regards to the latency of this shift. The studies reporting an enhanced N60

component used brief 0.1-0.2ms electrical stimulation while this study and Kekoni et al. (1997) used longer vibration stimuli (200-300ms) and observed peak latency values ranging between 100-200ms. It is possible that the differences in latencies between the studies may be a result of the duration of the stimulus used, with longer duration stimuli resulting in increased peak latencies. This is supported by the results of experiment 6, which clearly show that the latency of the MN1 component increases with increasing stimulus duration.

6.6.2 The MP1 component

Some studies have reported the presence of a positive component following the initial negative shift (Akatsuka et al., 2005; Shinozaki et al., 1998) but another has not (Kekoni et al., 1997). However illustrations provided by Kekoni et al suggest a possible positive enhancement between 200-300ms, though the authors did not actively examine this. Akatsuka et al. (2005) noted that the positive component was not present when the paired inter-stimulus time of the deviant stimulus was longer than that of the standard. They proposed that this related to the findings of the two-point discrimination threshold (TDT) studies reported by Hoshiyama et al. (2004), who found that the ascending TDT was higher than the descending TDT. In possible relation to this, it was observed that there was better discrimination between the stimulus pairs when the longer duration stimulus was presented first. In apparent contrast to the findings of Akatsuka et al. (2005), these results showed that the MP1 component was not present when the deviant stimulus was of a shorter duration than the preceding standard.

When a 20ms/70Hz stimulus was used as a frequency deviant clear MN1 and MP1 components were observed. However when this same stimulus was used as a shorter duration deviant a well formed MN1 was seen, but no reproducible

MP1 was present. This suggests that the MP1 component is not just a response to change but may be particularly sensitive to temporal changes. It may be that it was the perceived stimulus duration differences and not the within pair ISI differences that evoked the changes in the positive component reported by Akatsuka et al. (2005). They reported that at the shortest paired stimulus times subjects always perceived the two stimuli as one, while at the longest times the subjects always perceived two clear stimuli. The third stimulus pair they used was closer to threshold and was perceptually more ambiguous, but may still be felt as two different stimuli automatically (Akatsuka et al., 2005). It is possible that at the shortest paired stimulus times the stimulus was perceived as one longer duration stimulus while the pairs with the longer paired stimulus times were perceived as two shorter duration stimuli. If this were the case and if this positive component were indeed sensitive to duration differences, then the loss, or negative shift, of this positive component would occur when deviant stimulus is perceived as shorter than the preceding standard stimulus in a manner similar to the findings of this study.

6.7 Conclusion

There is clearly a mismatch response in the somatosensory system that fits many of the characteristics of a mismatch process (section 3.1) and these studies have further characterized a positive component that appears unique to the somatosensory system. Previous studies have reported conflicting results, in particular with regards to any positive component. The experiments in this chapter clarify the effect of stimulus duration on the somatosensory mismatch response, which has not been previously examined. This will have an impact as each study to date has used different types of stimuli, from very short electrical pulses to longer vibration. Also shown is that stimulus duration and order of presentation

has an effect on the response, an issue that has not previously been addressed but may have an important impact on future studies of the positive component. It is possible that the positive component may be an inherent part of the mismatch response, which is particularly sensitive to changes in the temporal characteristics of the stimuli, particularly the duration, rather than to differences in the threshold for detecting paired stimuli vs. unpaired stimuli as proposed by Akatsuka et al. (2005). The temporal sensitivity and scalp distribution of the MP1 suggests that it is a separate entity from the earlier negative component and may reflect a process that is specific to the somatosensory modality. Further study is needed to elucidate the properties of this component.

Chapter 7: Somatosensory discrimination responses from intracranial recordings in children

7.1 Introduction

The previous experiments examined scalp recorded SERP responses to deviations in either frequency or duration. In this study, the opportunity arose to repeat elements of those experiments with recordings from intracranial electrodes. Human intracranial recordings usually measure local field potentials, and can offer higher voltage responses and improved spatial resolution in contrast with scalp recorded ERPs, which are distorted due to spatially integrating properties of the skin, skull and cerebrospinal fluid (Taylor and Baldeweg, 2002). Intracranial ERPs (iERPs) usually appear as a response over a few adjacent electrodes and have steep amplitude gradients, suggesting close proximity to local cortical generators. The main advantage of iERPs is that it combines the temporal resolution of scalp ERPs with a spatial resolution comparable to the fMRI (section 1.5; Lachaux et al., 2003; Taylor and Baldeweg, 2002). However there are limitations to this technique because the insertion of the electrodes is based on clinical need and thus the electrodes are only applied to restricted areas of the brain.

The subjects participating in the intracranial recordings described in this chapter are children and it must be recognized that the electrophysiology of all sensory systems will show changes in latency and amplitude during development (section 2.2.2). In the past intracranial techniques have been successfully used to study aMMN in children (Liasis et al., 1999). There is no published data on somatosensory mismatch processing in children, but review of the literature on the paediatric aMMN suggests that this ERP response also changes in development.

As a child gets older, there are decreases in latency and increases in amplitude of the mismatch components, with the frontal and temporal aMMN components developing at different rates. These changes are reviewed in more depth in section 3.2.4.

7.1.1 Aims of this study

The purpose of this study was to extend the findings of chapter 6 using intracranial recording techniques to more accurately localize the MN1 and MP1 components and ascertain if there are differences in their distribution. It also provided the opportunity to examine possible differences between the responses to a frequency versus duration deviant, such as the topographical differences reported for the aMMN (Liasis et al., 2000).

As the intracranial patients who participated in this study were children, and there is no published data on sMMR responses in children, the same stimulus protocols were used to record SERPs from a control group of similarly aged children using scalp electrodes.

7.2 Experiment 8 - Intracranial recordings

7.2.1 Subjects

This study recruited 10 child subjects (median age 14 years, range 6-17 years, 3 males) who were patients in the telemetry ward at Great Ormond Street Hospital for Children, NHS Trust, London. All subjects had medically refractory epilepsy and were admitted for invasive EEG monitoring using sub-dural electrode arrays (SEAs) in order to identify the ictal onset zone, and its relation to functional cortex. There was no gross evidence of somatosensory impairment in any of the subjects. As the subjects were receiving different antiepileptic drugs and doses, the

influence of these was not specifically considered. The doses had usually been reduced at the time of testing, however this was not universal. Informed consent was obtained from both the subjects and their parents.

7.2.2 Methods

7.2.2.1 Stimuli

Construction and delivery of the stimulus was the same as outlined in section 5.3.2. The use of vibrotactile stimulation applied to the fingertips has previously been shown to be an acceptable method of stimulation with children (Holloway et al, 2000).

All ten subjects were presented with 4 blocks of 70Hz stimuli, such that blocks 1 and 3 were the same as were blocks 2 and 4. In blocks 1 and 3, 90% of the stimuli were 20ms and 10% were 250ms in duration. In blocks 2 and 4, 90% of the stimuli were 250ms and 10% were 20ms in duration.

Two subjects were also presented with 4 blocks of 20ms stimuli with deviations in frequency rather than duration. In blocks 1 and 3, 90% of the stimuli were 70Hz and 10% were 200Hz in frequency. In blocks 2 and 4, 90% were 200Hz and 10% were 70Hz in frequency.

7.2.2.2 Experimental procedure

The recordings were obtained 3-5 days after implantation and the session lasted 1-1.5 hours. The experimental setup is described in section 5.3.2

The presentation order of the stimulus blocks was randomised across subjects and 500 stimuli, with an inter-stimulus interval of 1000ms, were presented in each block with a minimum of two minutes between blocks. Stimulation was delivered to the fingers contralateral to the implanted hemisphere.

7.2.2.3 Continuous EEG recording

The recording method is similar to that described in section 4.3.3.4, however the sampling rate was 1000Hz and the recording was referenced to a distant electrode (on the grid or on one of the strips where present).

7.2.2.3.1 Electrode placement

SEAs consisting of platinum disks set 10mm apart in rectangular grids of 20-48 contacts, or in strips of 6-8 contacts, were placed over the left hemisphere in seven subjects and in three subjects over the right. The type, number, and position of the electrodes were determined by the location of the suspected epileptogenic zone in each subject, according to findings from clinical history, neuroimaging, neuropsychology, and scalp EEG recordings. See table 7.1 for the electrode positions for each subject. All ten subjects had electrodes over the mid and/or anterior parietal lobe. Eight had electrodes over various parts of the frontal lobe, two had strips of 6 contacts over the temporal lobe and two had strips of 6 contacts over the posterior parietal/occipital areas.

MR imaging of the brain was obtained in all patients before surgical implantation. In five patients, this was used to construct a three dimensional image of the child's cortex. A post-implantation computerized tomography scan was obtained showing the placement of the contacts. The 3D position of individual contacts was determined and superimposed on the 3D reconstruction of the cortex using commercial software (OsiriX, Astromed, USA).

Electrode Positions			
Patient number	**Hemisphere**	**N° of contacts and anatomical position**	**Lesion**
1	Left	20FP–6mF–6iF	Meningioangiomatosis - left frontal region
2	Left	48P–6pF	DNET - left parietal region
3	Right	48FP–6iF	Right frontal cortical dysplasia
4	Left	48F–6aP	Left frontal cortical dysplasia
5	Right	48PiF–6pPaO–6PT	Intractable epilepsy – right frontal focus
6	Left	48aPsTiF–6sF–6mF–6iF	Intractable epilepsy – left frontal focus
7	Left	48FP–6mF	Left fronto-central cortical dysplasia
8	Left	48P–6mF–6pPaO	Left parietal cortical dysplasia
9	Right	48PsT–6sF	Right central cortical dysplasia
10	Left	48PT–6mF–6T	DNET – left parietal region

F = frontal; T = temporal; P = parietal; O = occipital; s = superior; i = inferior; a = anterior; m = mid; p = posterior; N° = number.

Table 7.1: The number and anatomical location of the subdural electrode arrays and cortical lesions for each subject.

7.2.3 Results

In all cases, the EEG findings showed that the areas described in relation to somatosensory processing were not part of the ictal onset zone. The nomenclature used in chapter 6 will continue here, with the sMMR being composed of two components, MN1 and MP1. Table 7.2 shows the peak sMMR amplitudes and latencies for each subject.

7.2.3.1 Duration deviants

Well-defined focal ERPs were recorded over the parietal lobes of all ten subjects; however, subject 9 had several broken contacts, precluding further

analysis of those results. Allison et al. (1992) compared the most common components of long-latency somatosensory ERPs obtained from scalp recordings with those obtained from intracranial recordings and determined the correspondence between scalp components and cortical locations. Using their work as a guide, we have labelled the intracranial responses with the corresponding scalp nomenclature.

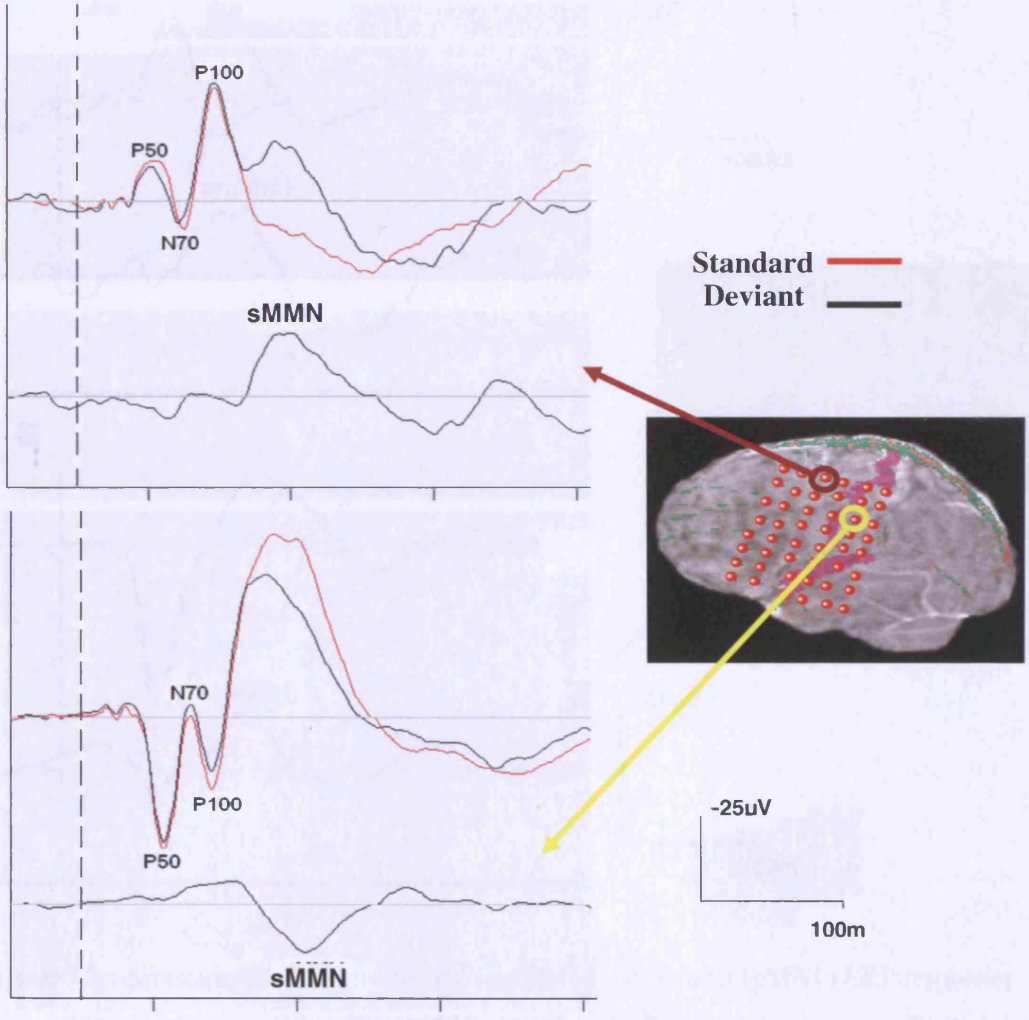


Figure 7.1: Sample ERP responses from subject 3 to a 20ms, 70Hz stimulus. Top waveforms: Overlying responses to the deviant (solid) and standard (dashed) stimuli. Lower waveforms: Difference waveform obtained by subtracting the standard from the deviant responses. Note that these responses phase reverse across the central sulcus. (At the bottom are 3D reconstructions of the cortices with superimposed SEAs. Similar images are used in subsequent figures.)

The ERP responses to both the deviant and standard stimuli were usually seen as a P50-N70-P100 complex over the post-central gyrus (BA1, 2, 3) and phase-reversing across the central sulcus (fig. 7.1). An N140 response was seen in six subjects and also appeared maximally over the post-central sulcus. It was more notable in the responses to the deviant stimuli.

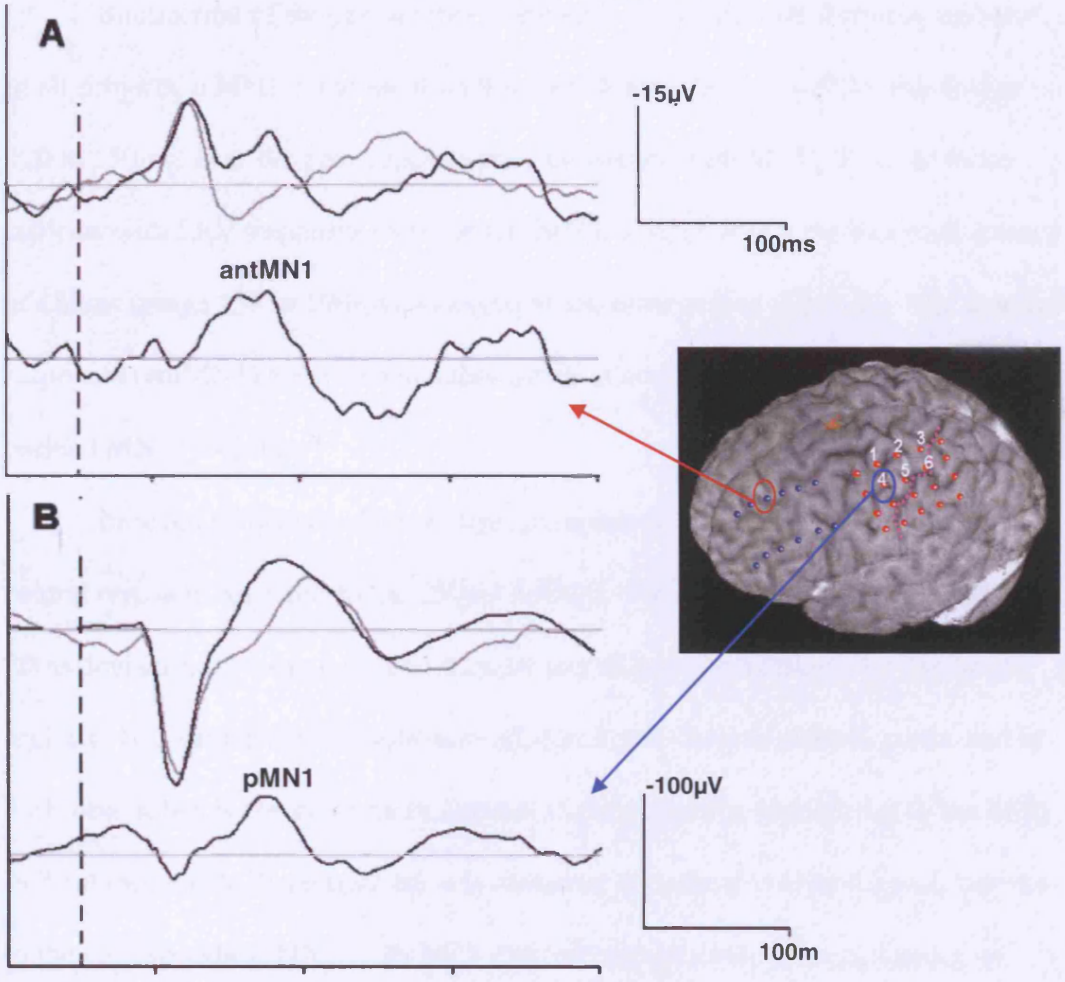


Figure 7.2: An example of the pre-frontal (antMN1) and parietal (pMN1) ERP responses from subject 1 in response to a 20ms, 70Hz stimulus. A) Pre-frontal responses. B) Parietal responses. Top traces (A and B): Dark responses are standard stimuli, light responses are deviant stimuli. Bottom traces (A and B): Difference waveform obtained by subtracting the standard from the deviant responses.

ERPs were also observed over the left middle frontal gyrus (MFG, BA46) in three subjects. In four subjects a P3b response was observed between 260-310ms over the parietal region with subjects 5 and 6 showing the best responses, which were seen maximally over inferior parietal area (BA40). Two subjects had small P3a responses over the frontal regions between 250 and 320ms.

Subtraction of the pre-deviant standard from the deviant response revealed, in all subjects, a MN1 component with a median peak latency of 134.5ms (range 120 to 150ms) over the post-central gyrus, consistent with SI (fig 7. 1). In those subjects with ERP responses over the left MFG, a MN1 with a median peak latency of 182ms (range 138 to 190ms) was seen in the same region (fig 7. 2). The anterior responses (antMN1) were considerably lower in amplitude and later than the parietal MN1 (pMN1).

In seven subjects a clear positive component, MP1, was observed in the central region in response to the 250ms deviant. No MP1 response was seen to the 20ms deviant nor was one observed under any stimulus condition over the frontal regions. In 5 subjects this component appeared over the post-central gyrus, and in 3 of these subjects the component appears slightly anterior and inferior to the MN1. In 2 subjects the MP1 component was observed over the pre-central gyrus, anterior to the corresponding MN1. The MP1 component had a median peak latency of 201ms (range 182 to 210ms) (fig. 7.3).

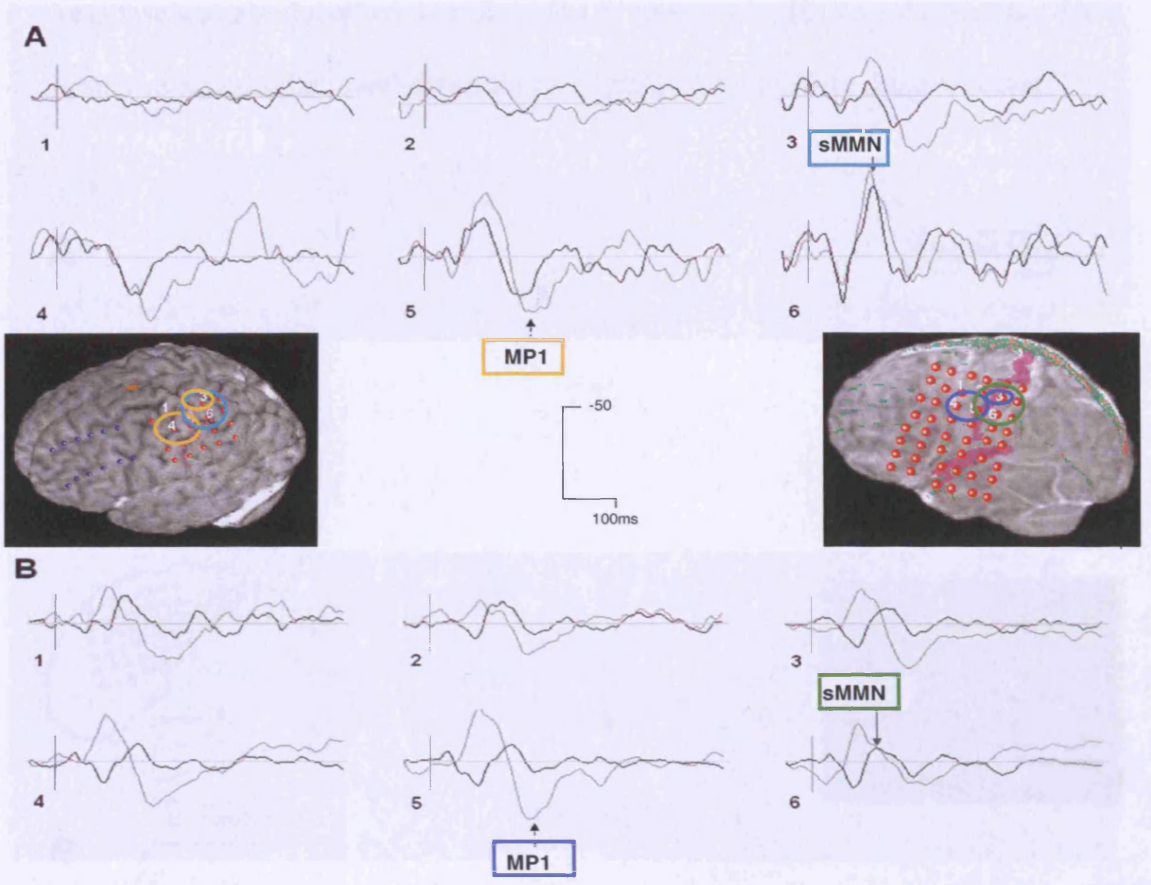


Figure 7.3: Subtraction waveforms showing the topographical differences between the MN1 and MP1 components of the mismatch response in two subjects. In both subjects the MP1 component appears over the pre-central gyrus, more anterior to the MN1, which is located over the post-central gyrus.

7.2.3.2 Frequency deviants

In the two subjects tested using both frequency and duration deviants, the ERP responses were similar in morphology with the P50, N70 and P100 components being consistent over the same electrodes. However the subtraction of the pre-deviant standard from the deviant response revealed that the MN1 and MP1 obtained from the frequency deviants appeared slightly earlier and appeared maximally in a more posterior position than the duration MN1 and MP1 (fig. 7.4). One subject had contacts over the frontal lobe and a separate antMN1, but no MP1,

response was also recorded over the MFG in response to frequency deviation. The response was similar in distribution and slightly earlier than the duration antMN1.

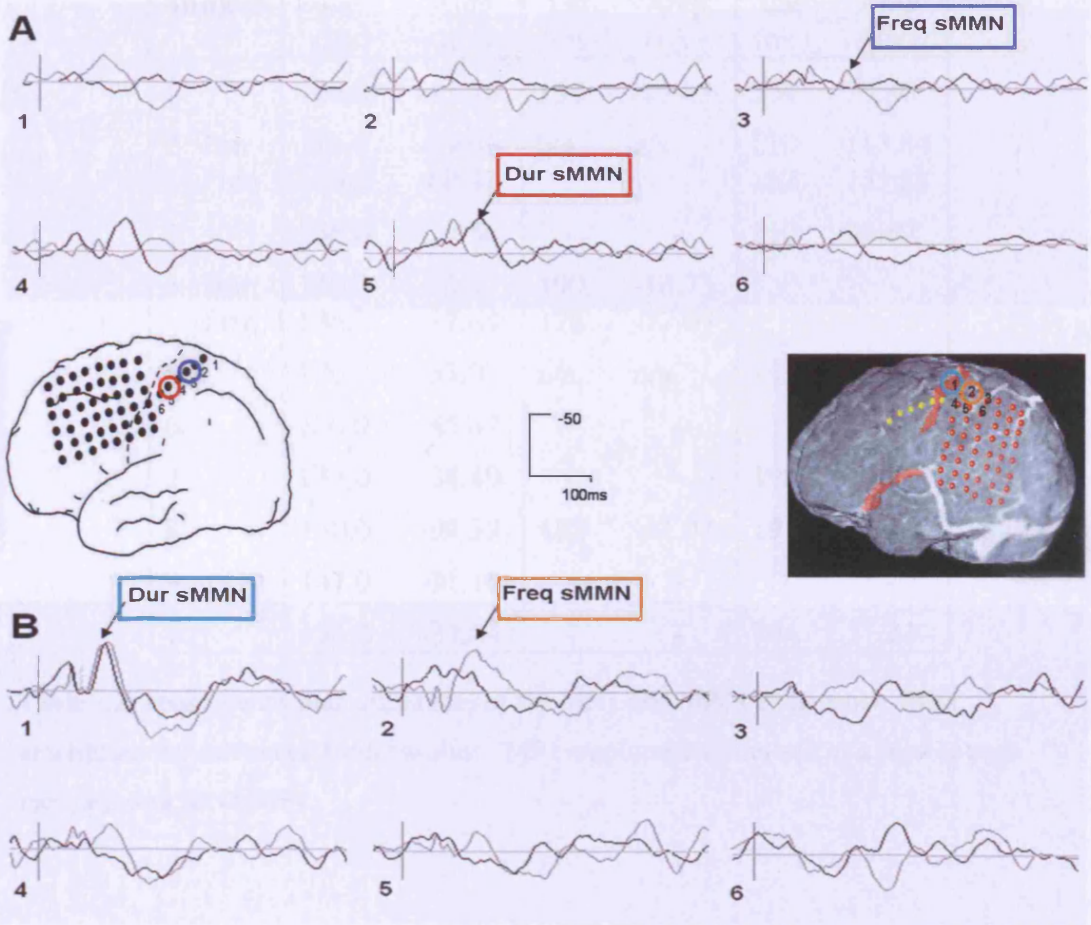


Figure 7.4: Subtraction waveforms showing the topographical differences between the sMMR responses to a frequency versus duration deviant in subjects 2 and 4. A schematic diagram is used to depict the SEA positions in subject 4 as a 3D reconstruction was not obtainable. In both subjects the frequency sMMN appeared more posterior than the duration sMMN.

Peak latency and amplitudes of the mismatch response						
Subject	MN1		antMN1		MP1	
	Lat (ms)	Amp (μV)	Lat (ms)	Amp (μV)	Lat (ms)	Amp (μV)
1	126.0	-45.86	138	-15.45	204	70.80
2 Dur	126.0	-49.66	n/a	n/a	210	113.84
Freq	120.0	-80.43			182	133.88
3	136.0	-15.56	-	-	210	23.69
4 Dur	140.0	-50.47	190	-18.73	-	-
Freq	136.0	-32.64	176	-17.09		
5	120.0	-53.07	n/a	n/a	191	55.65
6	150.0	-45.67	-	-	-	-
7	133.0	-34.49	-	-	198	52.45
8	130.0	-99.39	182	-31.92	195	151.40
9	147.0	-31.10	-	-	-	-
10	136.0	-33.04	-	-	204	51.27

Table 7.2: Peak latency and amplitudes of the MN1 and MP1 components. MN1 amplitudes are calculated from baseline. MP1 amplitudes calculated as a peak to peak measurement MN1/MP1.

7.3 Experiment 9 - Child controls

7.3.1 Subjects

Ten children (median age 10yrs, range 4-17yrs, 4 males) participated in this study. Informed consent was also obtained from both the subjects and their parents.

7.3.2 Methods

7.3.2.1 Stimuli

Section 4.3.3.2 describes the methods for stimulus construction and delivery. The same stimuli were used for duration deviations as is described above. No frequency deviations were presented.

7.3.2.2 Experimental procedure

The recordings were obtained using the same experimental setup as described in section 4.3.3.3 with the omission of the vacuum cast. The children were monitored for hand movement and stimulation position in a manner similar to what was done on the ward with the intracranial subjects. Stimulus presentation was as described above and the session lasted 1-1.5 hours.

7.3.2.3 Continuous EEG recording

The method of continuous EEG recording is described in section 4.3.3.4 with the exception of the sampling rate being 1000Hz.

7.3.2.3.1 Electrode placement

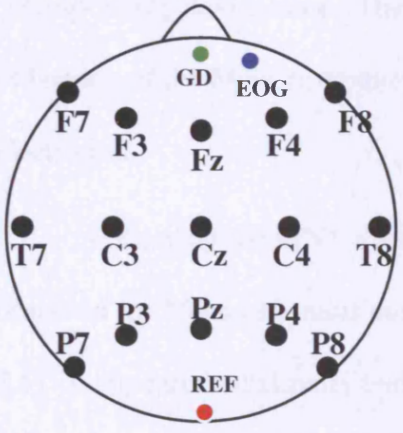


Figure 7.5: Schematic representation of the position of the scalp electrodes.

Continuous EEG data was collected using twenty-five Ag/AgCl electrodes that were applied based on a modified version of the International 10-10 system (figure 7.5).

7.3.3 Statistical analysis

The statistical analysis is described in chapter 6 with the factors used in the ANOVA being stimulus (deviant, standard), electrode (P7, P8, C1, Cz, C2), and duration (20, 250ms).

7.4 Results

The results were similar to those of the adults described in chapter 6. A clear negative shift in the ERP responses to the deviant stimuli was observed between 100-200ms following stimulus onset (MN1) (fig. 7.6). This was most marked over the central region. ERPs were averaged across the deviants and the immediately preceding standards. Statistical analyses confirmed that the mean amplitude between 100-200ms of the deviant response was significantly higher than that of the corresponding standard response ($F(1,4)=49.65$, $p<0.001$). A difference waveform was then obtained by taking the standard response from the corresponding deviant one. There were no significant differences in the amplitude or latency of the MN1 component between the different durations or between the electrodes.

Following the MN1 a positive shift between 170-270ms (MP1) was observed for 250ms stimulus durations, but not the 20ms stimulus duration (fig. 7.6). It appeared maximally over the vertex, with a contralateral emphasis. Statistical analyses confirmed that the mean amplitude between 175-250ms of the deviant response was significantly higher than that of the corresponding standard

response ($F(1,4)=31.52$, $p<0.001$). There was also a significant interaction between the stimulus type and duration ($F(1,110)=16.77$, $p< 0.001$, $\varepsilon = 0.001$). Paired samples t-tests showed significant differences between the deviant and standard responses for the 250ms stimuli ($t(59)=6.13$, $p< 0.001$) but not for the 20ms stimuli ($t(59)=1.16$, $p =0.249$). There were no significant differences in peak latency or amplitude of the subtraction waveform between electrodes.

T-tests comparing the mean latencies and amplitudes of the MN1 and MP1 components were performed between the child controls and the adult subjects from chapter 6. Despite a tendency for larger component amplitudes in the child group, no significant differences were found.

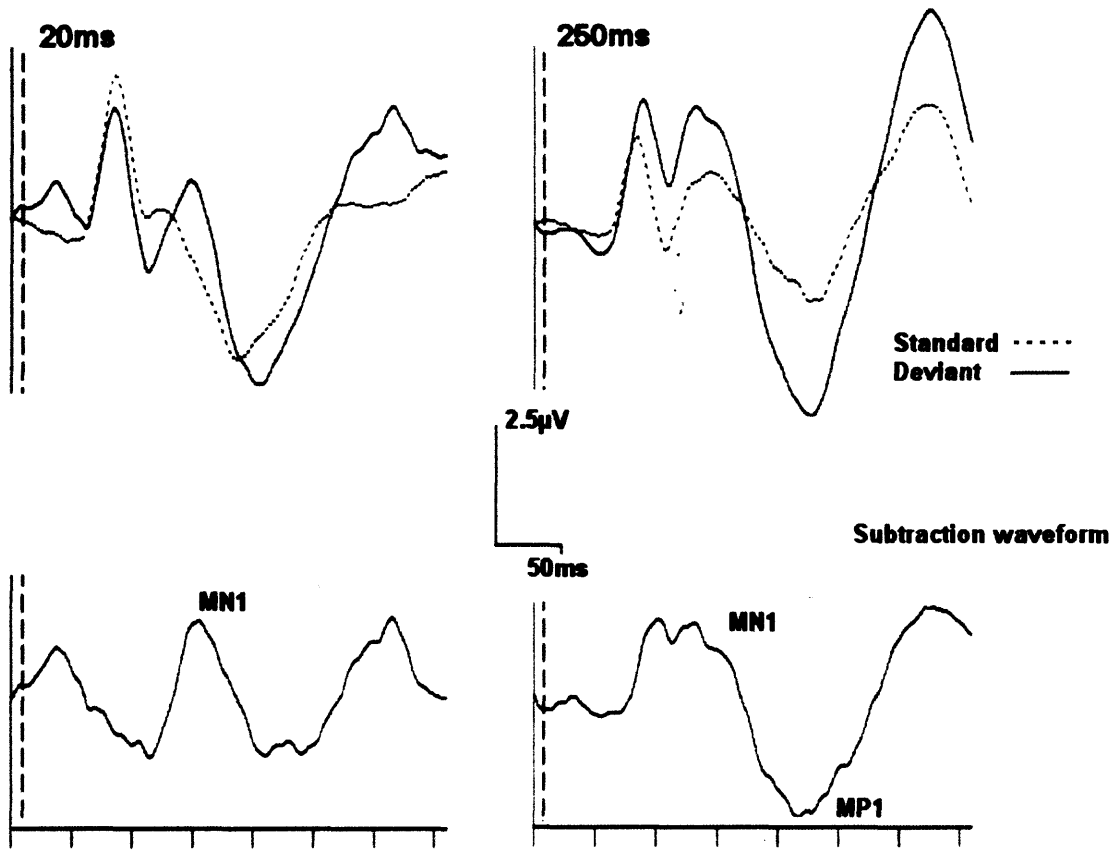


Figure 7.6: Grand averaged responses at Cz to the deviant and pre-deviant standard stimuli at 20 and 250ms in the child subjects. The solid lines are the deviant responses; dashed lines are the standard responses. The subtraction waveform is shown below. Note the lack of MP1 at 20ms stimulus durations

7.5 Discussion

The present study demonstrated that clear somatosensory mismatch ERPs to both frequency and duration deviants might be recorded from parietal and frontal regions in children in the absence of an active attention task. In addition there were differences in the distribution between the sMMR to frequency deviants and the sMMR to duration deviants. The results from the child control studies suggest there are no large differences between the child and adult results. However the small number of subjects and large age range preclude any definitive conclusions on possible maturational changes, which may occur in the sMMR.

7.5.1 The parietal sMMR

7.5.1.1 MN1 component

The MN1 component appeared at the same contacts as the P50 main component, over the post-central gyrus, which is consistent with the findings from the scalp recordings obtained from both the adults and child controls. This is suggestive of an SI generator, which has been proposed previously in the literature (Kekoni et al., 1997) and would be in keeping with a recent fMRI study by Preuschhof et al. (2006), which has implicated the human SI in the encoding process of vibrotactile working memory.

7.5.1.2 MP1 component

In addition to the MN1 component, a MP1 component was observed over both hemispheres in 8 intracranial subjects and in all 12 of the child controls. The MP1 occurred in response to the 250ms deviant stimuli but not the 20ms deviant

one. This is consistent with the adult findings reported in chapter 6, where the positive component was not observed when the deviant was shorter than the preceding standard.

The topography of this component was more variable than the MN1. No significant differences in topography were found between the MN1 and MP1 components in the child controls, but among the intracranial subjects, in 5 out of 7 it appeared maximally at contacts slightly more anterior and inferior to the MN1 component. The topography and sensitivity to the temporal characteristics of stimulus presentation suggests that MP1 may have a cortical generator different to that of the MN1, possibly within the ventral premotor cortex. Schubotz et al. (2003) and Schubotz and von Cramon (2001) have suggested that the ventral PMC might be related to the processing of temporal patterns independent of modality. Furthermore fMRI has implicated this region in frequency processing of vibrotactile stimuli (Preuschhof et al., 2006). Other possible locations lie within SII or the pre-central gyrus, both of which have both been implicated in vibrotactile discrimination processing (Preuschhof et al., 2006; Kekoni et al., 1997).

7.5.1.3 Duration sMMR vs. frequency sMMR

Comparison of the topography of the frequency elicited sMMR and duration elicited sMMR was made in two intracranial subjects. Although the spatial resolution was limited by the configuration of the SEAs, there is a clear difference in the topography of the two responses, with the frequency sMMR appearing closely adjacent to, but more posterior than, the duration sMMR. Similarly, separate aMMN generators for frequency and duration have been reported within the temporal lobe and it was suggested that this might indicate a mechanism for fast parallel processing (Liasis et al., 2000). If this is the case, such

parallel processing is likely to exist in other sensory modalities, and may be characteristic of early sensory processing.

7.5.2 The frontal sMMR

The antMN1 was observed over the left MFG in three intracranial subjects, and these responses were of considerably lower amplitude than those recorded over the parietal region. No reliable antMN1 responses were observed in the scalp recordings of the child controls, which is consistent with the data obtained for the adult subjects in chapter 6.

A large number of neuroimaging and intracranial studies have reported a modality independent parietal-frontal network. This is activated during oddball tasks and thought to be involved in directing attention to novel events (Ardekani et al., 2002; Huang et al., 2005; Linden et al., 1999; McCarthy et al., 1997). The dorsolateral prefrontal cortex (DLPFC) and MFG are part of this network. These regions are thought to be involved in the encoding and maintaining of a vibrotactile memory trace (Preuschhof et al., 2006) and the antMN1 may be a reflection of this activity. In addition, PET and fMRI studies have shown that auditory mismatch conditions will activate the MFG region, particularly in response to complex novel auditory stimuli (Doeller et al., 2003; Muller et al., 2002) and therefore the antMN1 may not be a specific somatosensory response, but reflect a pre-attentive component of the modality independent parietal-frontal network.

Although the frontal component was only observed over the left hemisphere bilateral sources cannot be excluded. As the locations of the SEAs are determined by the requirements of the surgical procedure recording locations are not always optimal.

7.6 Conclusions

The results of the intracranial study has provided further evidence suggesting that the MP1 component may have a cortical generator different from the MN1 components and may reflect a temporal sensory discrimination process unique to the somatosensory system. It has also provided evidence suggesting that there are different sMMR generators for duration and frequency discrimination, similar to that seen in the auditory system (section 3.2.2). In addition to the above, a prefrontal somatosensory mismatch response was also observed, something that has not previously been reported in the literature. The discovery of this component provides support for involvement of a parietal-frontal network in the encoding of somatosensory memories.

Previous ERP, MEG and fMRI studies have demonstrated that oddball paradigms, such as those used to study the MMN, evoke widely distributed activity in cortical and subcortical neuronal networks, usually associated with the P300 (McCarthy and Wood, 1987; Wang et al., 2003) and a number suggest that, in addition to sensory specific cortical generators, there is a modality independent frontal – parietal network that is commonly activated during auditory, visual and somatosensory oddball tasks (Ardekani et al., 2002; Huang et al., 2005; McCarthy et al., 1997). Many of these same regions have also been implicated in tactile working memory (Preuschhof et al., 2006), with the left pre-frontal and parietal regions being particularly activated during the short-term storage of somatosensory information (Stoekel et al., 2003). As the cortical distribution and latency of the antMN1 response are consistent with MFG involvement reported above in the active oddball tasks, we speculate that the antMMN responses may be part of this network.

If the sMMR reflects haptic memory such as the aMMN is thought to reflect echoic memory (section 3.2) then this fronto-parietal network may be involved in the neural processes of sensory to working memory encoding in the somatosensory system. The initial somatosensory discrimination (detection of stimulus change) appears to occur in the parietal region as indexed by pMN1/MP1 and this is then followed by the later antMN1 response in the pre-frontal region; an area particularly linked with working memory. Both of these components had an earlier timing and different distribution to the P300 (section 7.2.3), which is consistent with the premise they reflect pre-attentive processing. In the auditory system a pre-frontal aMMN potential is also observed and is thought to be particularly involved in involuntary attention switching (section 3.2.3). If mismatch processing is similar between the different sensory modalities, then it is possible the somatosensory pMN1 reflects the neuronal processes involved in discriminating between stimuli and this is then followed by the antMN1 that may reflect processes involved in switching attention to these changes; a precursor to the encoding of information from sensory memory to working memory (section 1.4.1).

Given the indications of multimodal processing in the prefrontal regions reported in the studies mentioned above, it is plausible that pre-frontal aMMN and the antMN1 potentials reflect the same process. In addition, there are indications that feedback mechanisms exist between the pre-frontal regions and the primary sensory areas. For example, a study examining patients with lesions in the DLPFC showed poorer auditory discrimination and decreases in the amplitudes of the aMMN (Alain et al., 1998). It is likely there are interactions between the mismatch processing of different modality sensory input and that it may be possible to

measure these interactions using mismatch ERPs. This would aid in the determination of how individual sensory inputs interact to form a cohesive perception of the environment. This is the fundamental reasoning underlying the study described in the next chapter.

Chapter 8 : Multisensory interactions in auditory and somatosensory discrimination processing

8.1 Introduction

8.1.1 Multisensory integration

The tasks we perform every day rely on information conveyed to the different sensory modalities, yet it is obvious that we perceive the world as an integrated representation of these inputs and not as separate information. This unification of perception reflects a fundamental component of cognition and behaviour and thus the modulation and integration of sensory input must be a basic task of the central nervous system. The integration of inputs from multisensory sources can function to reduce perceptual ambiguity and speed responsiveness (Stein and Meredith, 1993). The nature of this integration, such as how, when and where in the cortex this information is combined, is still only imperfectly understood.

Since the 1960s it has been accepted that sensory processing occurred in a hierarchical fashion from primary to secondary to association/heteromodal cortex. However more recent evidence has challenged this supposition and suggests a more divergent, parallel processing (for review see Mesulam, 1998). Related to this has been the prevailing view that multisensory integration is reserved for higher cortical levels and occurs at a 'late' stage of cortical processing following enhancement of the unisensory signals in the modality specific cortical regions (e.g. Okajima et al., 1995; Schröger and Widmann, 1998). This assumption has been largely based on the relative synaptic distance of the heteromodal zones from the primary sensory cortices seen in animal studies but may also arise from the tradition of studying individual sensory modalities in isolation. More recent

evidence from animal, imaging and electrical studies suggest this model may be somewhat simplistic and that multisensory integration can occur much earlier and in areas usually held to be unisensory.

8.1.1.1 Behavioural studies

There are two main conditions that determine intersensory binding and result in crossmodal effects; these are synchronicity and spatial correspondence. Early studies of crossmodal effects demonstrated that a stimulus with no meaningful relationship other than temporal proximity can increase the reaction time in a target detection task, a phenomenon labelled the 'redundant target effect' (Gielen et al., 1983; Hershenson, 1962; Shroger and Widmann, 1998). The most recent explanations for this are based on 'coactivation' models, in which the signals from the different sensory modalities are integrated prior to initiation of the motor response (Miller, 1991; Molholm et al., 2002).

In addition to temporal proximity, close spatial proximity is also important in producing crossmodal effects and interaction effects leading to improved responsiveness are largest when there is temporal and spatial concordance (Calvert and Thesen, 2004). In contrast, a small temporal and spatial discordance in crossmodal cues will result in what appears to be crossmodal inhibition, eliciting a response significantly less effectively than that seen with unimodal stimuli (Sekuler et al., 1997; Stein et al., 1989).

Sensory integration may also be influenced by cognitive factors, such as semantic congruence. The sound of a barking dog corresponding spatially and temporally with a visual image of a cat will not generally elicit the perception of a barking cat, however in a movie theatre sounds coming from a speaker accompanying images of people will elicit the perception of speech arising from

the images, an example of the ventriloquist effect (Bertelson and Aschersleben, 1998). These examples illustrate the influence of semantic congruence on the synthesis of multisensory inputs. In addition, multisensory inputs concerning object identification may combine to produce a perceptual outcome that was neither actually seen nor heard. Audio-visual interactions will cause the McGurk effect, in which the dubbing of an audible syllable |ba| onto an image of a speaker mouthing a different syllable |ga| to typically result in the perception of |da| (McGurk and MacDonald, 1976). Similarly, audio-somatosensory interactions may result in the 'parchment skin illusion' in which enhancement of high frequency component (>2kHz) of sounds produced by rubbing palms together results in subjects experiencing the sensation of having a leaf of parchment paper between their hands (Jousmaki and Hari, 1998). These illusions occur because the contextual information from the two sensory systems is complementary and thus may also tolerate more temporal and spatial disparity than two inputs that share no contextual information, such as demonstrated by the ventriloquist effect.

8.1.1.2 Neuroanatomical studies

The main principles of sensory integration have been largely based on studies of multisensory processing in the superior colliculus of anaesthetized cats (for review see Stein and Meredith, 1993). Single unit recording of the superior colliculus have shown overlapping sensory receptive fields, one for each of the sensory modalities (auditory, visual, and somatosensory) to which they respond. The response of these neurons can be significantly enhanced beyond that expected by summation by two or more sensory inputs occurring in close temporal and spatial proximity (Stein and Meredith, 1993) and because the output differs so much from the individual responses, there is the assumption that the information

obtained from the two sources has been combined to form a new output signal (Stein et al, 1994). This is the basis of multisensory integration. It has been observed that this facilitation of the neuronal response is strongest when the individual stimuli are minimally effective in eliciting a neural response, this principle is known as 'inverse effectiveness'. In addition, there is the principle of 'response depression' in which temporally and spatially disparate stimuli can decrease in the neuronal response (Stein and Meredith, 1993).

A large number of "heteromodal" or "association" regions of cortex have been identified and these include the anterior portions of superior temporal sulcus (Neal et al., 1990; Watanabe and Iwai, 1991), temporo-parietal association cortex (Desimone and Ungerleider, 1986), parietal cortex (Lewis and Van Essen, 2000; Linden et al., 1999) and prefrontal and premotor cortex (Graziano et al., 1999; Watanabe, 1992). In addition to these areas, a number of studies have shown that regions previously thought to be unisensory are also involved in multisensory processing. A series of studies performed by Schroeder et al. (2001, 2002) observed auditory-somatosensory co-representation within the posterior auditory cortex at very short latencies. Recordings of the laminar response profiles showed that both the auditory and somatosensory inputs had characteristic feed-forward patterns while visual inputs had a feedback pattern. This suggests 'bottom-up' multisensory processing that occurs earlier in the hierarchy of sensory processing than traditionally thought. Functional imaging studies in humans have shown similar multisensory effects in classically unisensory regions (Calvert et al., 1999; Foxe et al., 2002; Macaluso et al., 2000).

8.1.2 Electro-magnetic recordings and sensory integration

Over the last few years a number of MEG and EEG studies have shown surprisingly early crossmodal interaction effects and the scalp topography of these effects support the neuroanatomical and neuroimaging findings indicating early integration of sensory information in 'unisensory' cortex. Early (<100ms) and late (≥100ms) multisensory effects have been observed using audio-visual (Molholm et al., 2002; Giard and Peronnet, 1999), audio-somatosensory (Foxe et al., 2000) and visual-somatosensory (Lam et al., 1999) stimuli.

8.1.2.1 Auditory and somatosensory interactions

An early ERP study by Okajima et al. (1995) reported auditory interaction effects on the SERPs at 120-130ms. This was followed a few years later by a MEG study using vibrotactile stimuli that showed activation of the auditory cortex of a congenitally deaf adult, suggesting that the auditory cortex may have the capability of multisensory processing of tactile stimulation (Levänen et al., 1998). Since then there have been a number of studies using MEG and ERPs to examine the crossmodal effects between auditory and somatosensory stimuli, sometimes with contrasting results. An ERP study by Foxe et al. (2000) reported SERPs to electric stimulation of the left wrist, to tones presented to the left ear and to both simultaneously. They found auditory-somatosensory interaction effects with an onset of about 50ms over the contralateral somatosensory cortices and a later effect of 70-80ms over the posterior auditory cortex. These findings were consistent with those reported in studies of the monkey neocortex (Schroeder et al., 2002). A more recent study has examined the tolerance of the crossmodal effects to spatial disparity using a behavioural task and SERPs to vibration stimuli and white noise, either alone or simultaneously. This study also reported interaction effects as early

as 50ms, but localized them to the auditory association areas contralateral to the side of somatosensory stimulation regardless of the location of the auditory stimulus (Murray et al., 2005). Both the above studies reported an enhancement of the SERP response greater than summation of the constituent unisensory responses.

Two MEG studies also report clear interactions effects. A study by Lükenhöner et al. (2002) used unilateral tactile pressure pulses and binaural tones, either separately or simultaneously and reported clear audiotactile interactions at later latencies of 140 and 220ms. Contrary to the above studies, they found that the response to the simultaneous audiotactile stimulation was weaker than the sum of the responses to the auditory and tactile stimuli alone. However the stimuli used in this study were temporally in congruence but not spatially. This spatially disparity may account for the inhibition interaction observed in a manner similar to that reported in animal studies (Stein and Meredith, 1993). The second MEG study (Gobbelé et al., 2003) expanded on this one and used temporally and spatially coincident electrical pulses to the wrist and tones delivered alternately to the left and right sides. Early interactions effects were observed at 75-85ms, somewhat later than those reported in the EEG studies, as well as a later effect at 105-130ms. The early effects were found to occur in the contralateral posterior parietal cortex and the later interactions in the contralateral parietal operculum between SII cortex and the auditory cortex. They also noted that the response to the audio and tactile stimuli together were similar in morphology to the tactile-only responses. They proposed that this was due to suppression of the auditory responses most likely resulting from the greater salience of the tactile stimuli.

There are some contrasts between the results of the above studies, specifically the MEG studies reported interactions occurring at longer latencies

than the EEG studies and there is controversy on the location of the generators of these interactions, i.e. the auditory cortex or SII area. In addition to the variance that arises from the differences in sensitivity of the MEG and EEG to tangential and radial generators, differences in experimental paradigm and source analysis are most likely to account for these discrepancies between the studies. The studies all differ in the spatial similarity and temporal coincidences of the study with some using spatially aligned or misaligned stimuli (Lütkenhöner et al., 2002; Murray et al., 2005), while others have varied in unilateral or bilateral stimulus presentation (Foxe et al., 2000; Gobbelé et al., 2003). The perception of the stimuli may also have differed; only Murray et al., 2005 used a behavioural task to determine if the stimuli were perceived as separate or conjoined. If the perception of the stimuli is as separate entities it may be possible that one would be given greater salience over the other, as conjectured by Gobbelé et al., 2003. Thus it may also be possible that the interactions that are recordable may alter in topography depending on the salience of the stimuli used. Also of note is an anticipatory slow-wave that appears with fixed or predictable timing between successive stimuli which has been reported in studies examining visual-auditory multisensory interactions (Molholm et al., 2002; Teder-Salejarvi et al., 2002). It is likely that a similar potential exists with auditory-tactile interactions and this may compromise the comparison between the responses of the combined audio-tactile stimulus and the summation of the individual stimuli in attended paradigms.

8.1.2.2 Crossmodal effects on the aMMN

There are only a few studies published examining the effects of multisensory integration on the MMN and all of these have involved audio-visual interactions. Most of these studies have found that, in the context of an

irrepressible audiovisual sensory illusion, such as the McGurk effect or the ventriloquist effect, visual deviants will elicit an aMMN (Ventriloquist effect: Colin et al., 2002a, Stekelenburg et al., 2004; McGurk effect: Colin et al., 2002b, Colin et al., 2004). Earlier work by Sams et al. (1991) found no evidence of an aMMN in response to only visual variations of the audiovisual stimulus and it was postulated that this effect was much reduced in the absence of a strong sensory illusion.

More recent work by Besle et al. (2005) has examined the effects of the interactions between auditory and visual (or both) deviations in nonspeech audio-visual stimuli without a strong sensory illusion. They compared the scalp topographies of the MMNs and found, contrary to what occurs in audio-visual illusions, that each unimodal deviant elicited a sensory specific MMN and that the MMN to the conjoined audio-visual deviants included both sensory components. However the visual MMN alone, in the context of joint audio-visual stimuli, was different from that obtained in a visual only paradigm and the MMN to the conjoined stimulus was different from the sum of the two sensory specific MMNs. This suggests that change detection mechanisms in the auditory and visual systems are not completely independent processes.

The visual context accompanying an auditory stimulus will also influence change detection in the auditory system. A study by Ullsperger et al. (2006) reported that a contextually aberrant visual deviant will affect the ERP elicited by identical standard sounds, producing a MMN. The authors argued that the visual context affected the auditory input and this led to a mismatch response. However examination of the published results suggests another interpretation. A clear mismatch waveform superimposed on a clear N2-P3 component can be observed in

response to the sound deviants, but the responses to the visual deviants do not show the same waveform or N2-P3 complex. These responses show an enhanced N1 component followed by a late slow wave. The statistically significant amplitude difference between the standard and deviant responses may only reflect the enhanced N1 component. Thus while it appears there may be some interaction between visual context and auditory ERPs, it is still debateable, from this data, whether visual context actually influences auditory sensory memory.

8.1.3 Aims of the study

The aim of this study was to determine if the presentation of spatially and temporally concordant auditory and somatosensory stimuli would result in an interaction effect between the auditory and somatosensory discrimination processes as reflected by ERP mismatch responses. Simple tones rather than more complex speech syllables were used as it seemed essential to try and balance the complexity of the auditory and somatosensory stimuli in order to minimize any possible effect stimulus complexity may have on the interactions between the two modalities. The interaction responses to the standard auditory and somatosensory stimuli are also examined to ascertain if the responses obtained using these techniques are consistent with those previously reported in the literature.

8.2 Subjects

A group of 25 subjects participated in the experiment (ages 21-54 yrs, 11 males) and all were right-handed. From this group, 15 subjects (mean age 29 yrs) had testing performed on their right hand (Group 1) and 10 subjects (mean age 25 yrs) had testing performed on their left hand (Group 2).

8.3 Methods

8.3.1 Stimuli

The methods for stimulus construction and delivery are described in section 4.3.3.2. As in previous experiments an odd-ball paradigm was used.

The somatosensory stimuli were the same as one used in section 6.3.2.2, 20ms duration with a 70Hz standard and 200Hz deviant. The auditory stimuli were generated by the same source as the somatosensory stimuli but the signal was sent to an amplifier located 50cm from the subjects' ear. A sound level meter (Kamplex SLM-3 type 2, P.C. Werth Ltd) was used to ensure both the 70Hz standard and 200Hz deviant had an equal intensity of 70dB.

The stimuli were presented unilaterally in each of three conditions, somatosensory stimuli alone (with auditory white-noise masking), auditory stimuli alone or the dual presentation of both types of stimuli. Each condition was presented twice and the results of each corresponding trial were compared for reproducibility. A total of 1500 stimuli were presented for each condition, with 150 deviants. In the dual stimulus condition the auditory and somatosensory stimuli were presented simultaneously to the same side of the subject, thus keeping both temporal and spatial congruence.

8.3.1.1 Experimental procedure

The general experimental setup is the same as described in section 4.3.3.3 with one exception, instead of watching a video the subject was required to perform a more active distraction task. The subjects were tested in a single recording session lasting 2-2.5hrs with a 10minute break in the middle. The stimuli

were presented with an ISI of 1000ms and a standard probability of 90% and a deviant probability of 10%.

8.3.1.2 Distraction task

In order to distract the subject from the stimuli more completely than a soundless video might, a distraction task involving either simple arithmetic or object matching both requiring a push button response was used. A monitor set 1.5m from the subject displayed either a series of simple math equations or a series of images and the subject was required to push a button if the answer to the equation or the image matched the target. The distraction task was randomly matched to the stimulus condition for each subject and the timing of the image presentation was offset and pseudo-randomised so as not to time-lock with the stimulus presentation.

8.3.1.3 Continuous EEG recording

The electrode placement and method of recording the continuous EEG are the same as those described in section 4.3.3.4 with the addition of electrodes in the M1 and M2 positions.

8.3.2 Offline analysis

Remontaging and epoch construction was performed as described in chapter 4. Then the averaged epochs for all standards, the pre-deviant standard and the deviant stimuli were obtained for each condition. In order to examine interaction effects between the auditory and somatosensory stimuli, the auditory (A) and somatosensory (S) standard responses were added together (A+S=AS) and compared with the dual (D) standard responses. Mean area amplitudes were obtained over the following three time windows (60-110ms; 120-150ms; 170ms-

220ms). A subtraction waveform was then obtained by subtracting AS from D. The electrodes showing the largest interaction responses in the grand average were then chosen for further analysis. The peak latency and amplitudes of the largest deflection in the above time windows were measured and compared with the prestimulus noise level. They had to exceed ±1 SD to be accepted as a genuine signal. Similar techniques have been used previously (Gobbelé et al., 2003; Foxe et al., 2000) but it should be noted that this method will not be sensitive to regions of purely multisensory convergence in which the responses between the two sensory modalities might occur but sum linearly.

To examine the interaction between mismatch responses of the two sensory modalities, the pre-deviant standard and deviant responses of each condition were compared and a subtraction waveform obtained showing the mismatch response to each of the three stimulus conditions. Then the auditory and somatosensory mismatch responses were added together (ASm) and compared to the dual mismatch response (Dm). A second subtraction waveform was obtained by subtracting ASm from Dm. Mean amplitudes were obtained for the standard responses, AS and D, and mismatch responses ASm and Dm. Peak amplitudes and latencies were identified for the main component of the corresponding difference waveforms. A previous study by Besle et al. (2005) used a similar method to examine interactions between aMMN and visual MMN.

8.4 Statistical analysis

Repeated-measures analysis of variance (ANOVA) was applied with stimulus type (AS and D or ASm and Dm) and electrode (CP3, CP4, M1, M2, C1, C2, F7, F8). The Greenhouse-Geisser correction was used for the F values when the degrees of freedom were greater than 1 and the probabilities adjusted with the

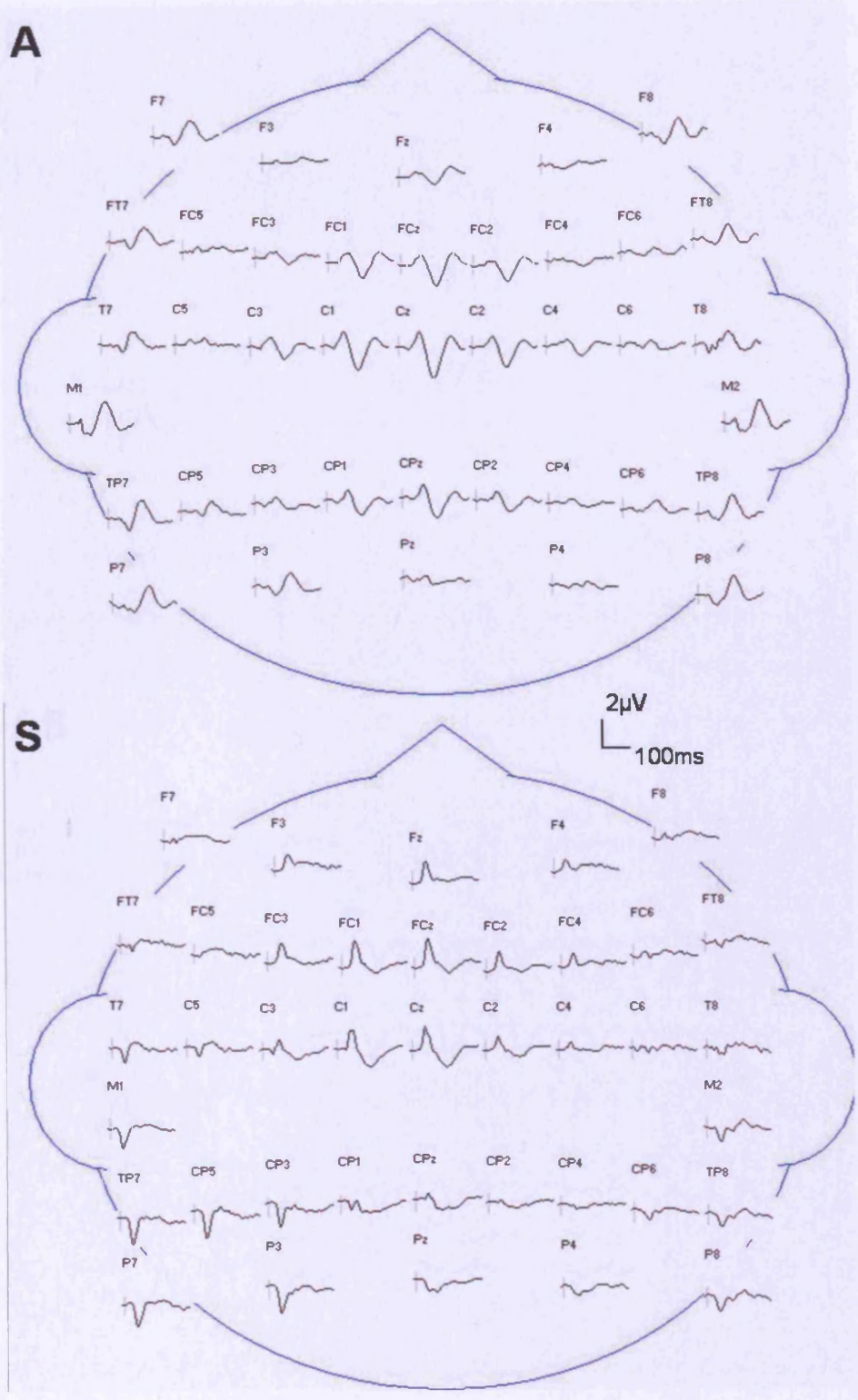
correction coefficient ε as necessary; the original degrees of freedom are presented for each analysis. Independent t-tests were used to compare the results between the groups tested on the right or left hand. The amplitudes of the subtraction waveforms were normalized according to a scaling procedure outlined by McCarthy and Wood (1985) in order to evaluate differences between the scalp distributions. Comparisons with the pre-stimulus noise level were made using a binomial test and signals rejected if they did not exceed ±1SD. The ASm and Dm were statistically assessed by *t*-tests comparing the averaged amplitude of the deviant minus standard difference waveform to zero in the 100-150ms time-window.

8.5 Results

8.5.1 Summed vs. concurrent auditory/somatosensory standard ERPs

8.5.1.1 Responses to A, S and D stimuli

Fig. 8.1 shows the group average responses to right-sided somatosensory (S), auditory (A) and dual (D) stimulation and the arithmetic sum of the somatosensory and auditory unimodal responses (AS). The S responses peaked at 74ms and 135ms over the contralateral parietal region and at 198ms bilaterally over the central parietal regions. The A responses contained main peaks at 69, 105, and 210ms over M2 and at 71, 113, and 216ms over M1. The D clearly contained a mixture of the two responses, with main peaks over the contralateral parietal region at 71 and 136ms, over the temporal regions 50, 90, 140 and 213ms and over the central/centro-parietal region at 204ms.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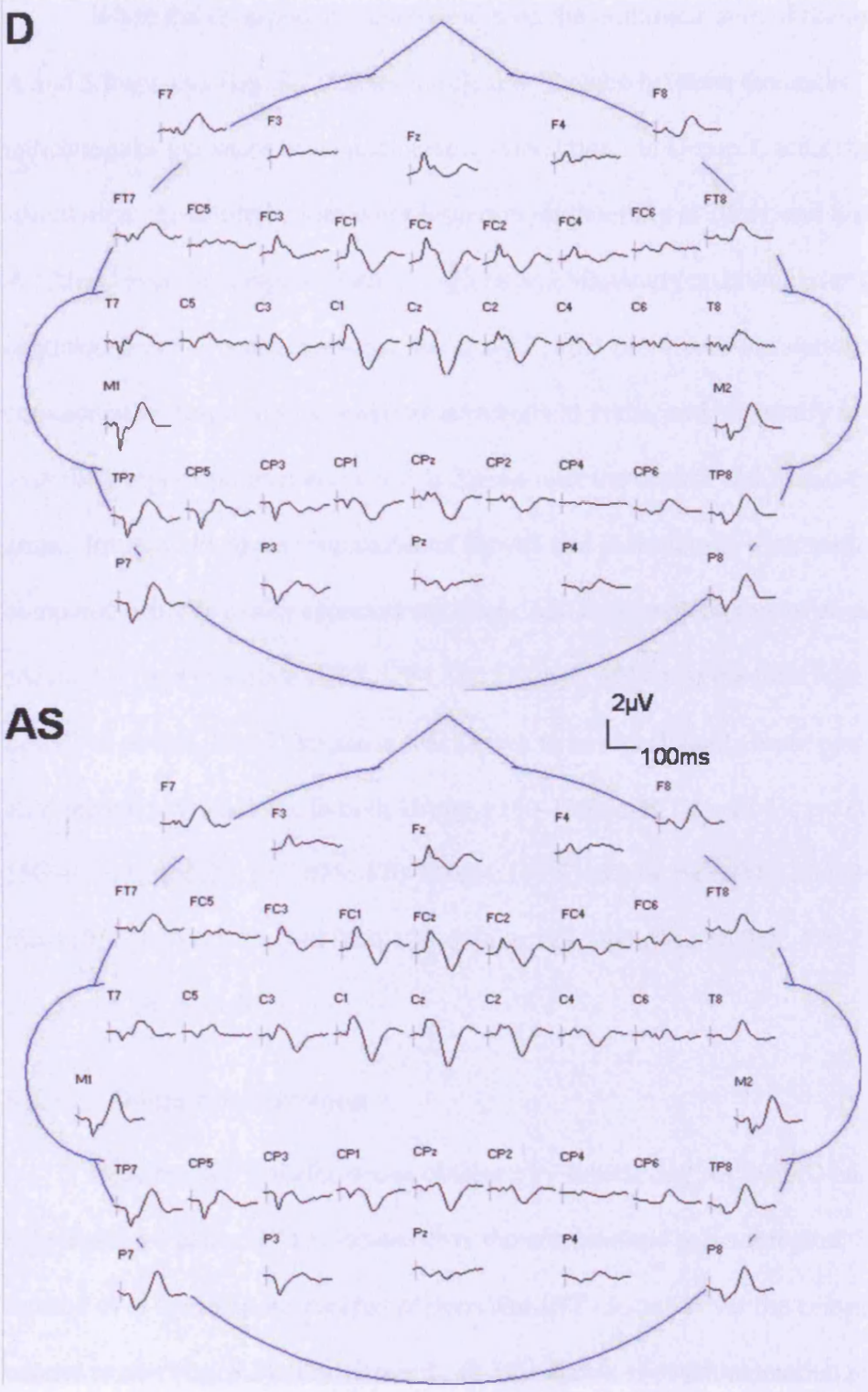


Figure 8.1: A schematic showing the scalp distributions of the responses to auditory (A) and somatosensory (S) unimodal stimulation, bimodal auditory and somatosensory stimulation (D) and to the sum of the A and S responses (AS).

When the D response is compared with the arithmetic sum of the unimodal A and S responses (fig. 8.2), there is a clear difference between the traces indicating the existence of an audiotactile interaction. In Group 1, after right-sided stimulation, these interactions were largest contralaterally at 70ms, and bilaterally at 125ms, over the temporo-parietal regions and bilaterally at 210ms over the central and fronto-central regions. In Group 2, after left-sided stimulation, the corresponding responses peaked contralaterally at 90ms, and bilaterally at 136ms over the temporo-parietal areas and at 200ms over the central and fronto-central areas. Initially the mean amplitudes of the AS and D responses were statistically compared using two-way repeated measures ANOVA, with factors of stimulus type (AS and D) and electrode (CP3, CP4, C1, C2, M1, M2) over the time windows described above. The D response was shown to be significantly more positive over all three latency windows in both Group 1 (60-110ms: $F(1,5)=12.61$, $p<0.003$; 120-150ms: $F(1,5)=8.20$, $p<0.015$; 170-220ms: $F(1,5)=52.44$, $p< 0.001$) and Group 2 (60-110: $F(1,5)=11.20$, $p<0.008$; 120-150ms: $F(1,5)=6.88$, $p<0.028$; 170-220ms: $F(1,5)=54.78$, $p< 0.001$).

8.5.1.2 Subtraction waveform

A difference waveform was obtained by subtracting AS from D and revealed three peaks, INT1, located over the contralateral parietal region, INT2, located over the temporo-parietal regions and INT3 located over the central/fronto-central region (fig. 8.2). For Group 1, all 16 subjects showed interaction responses (D-AS) which exceeded significantly the prestimulus noise level ($p<0.05$, binomial test) at the fronto-central/central electrodes, in 13 subjects at the left and right mastoid electrodes (with 3 subjects showing opposing polarity) and in 14 subjects at the left temporo-parietal electrodes. For Group 2 all 10 subjects showed

interaction responses significantly exceeding the prestimulus noise level ($p<0.05$) at the fronto-central/central electrodes, 7 subjects at the left and right mastoid electrodes and 9 at the right temporo-parietal electrodes.

The peak amplitudes and latencies of each interaction component for the two groups are shown in table 8.1. INT1 was only reliably and significantly observed over the contralateral parietal region for both groups. There were no significant differences in the amplitude or latency between electrodes for INT2 or INT3 for either the left or right, however INT3 tended to show a stronger response over the left hemisphere. Comparison between the groups showed no significant difference in latencies for INT2 and INT3 or any difference in amplitudes for INT2. There was a significant difference between the amplitudes of INT3 ($t=3.40$, $p< 0.001$) with responses in Group 2 appearing significantly smaller at C2 ($t=3.08$, $p<0.005$) but not at C1 ($t=1.77$, $p<0.093$).

		Group 1		Group 2	
Comp	**Hemis**	**Lat (ms) ±SD**	**Amp (μV) ±SD**	**Lat (ms) ±SD**	**Amp(μV) ±SD**
INT1	contra	84.8 ±10.0	-0.96 ±0.718	92.6 ±16.9	-0.96 ±0.38
INT2	contra	134.0 ±8.5	-0.75 ±1.44	136.5 ±11.0	-1.04 ±0.37
	ipsi	137.6 ±8.5	-0.61 ±0.83	138.3 ±10.5	-1.05 ±0.43
INT3	contra	202.8 ±18.6	-1.55 ±0.61	207.3 ±19.2	-0.80 ±0.53
	ipsi	200.9 ±17.8	-1.41 ±0.70	209.9 ±17.6	-0.91 ±0.64

Table 8.1: Peak latency and amplitude values for the three interaction components of the D-AS subtraction waveform.

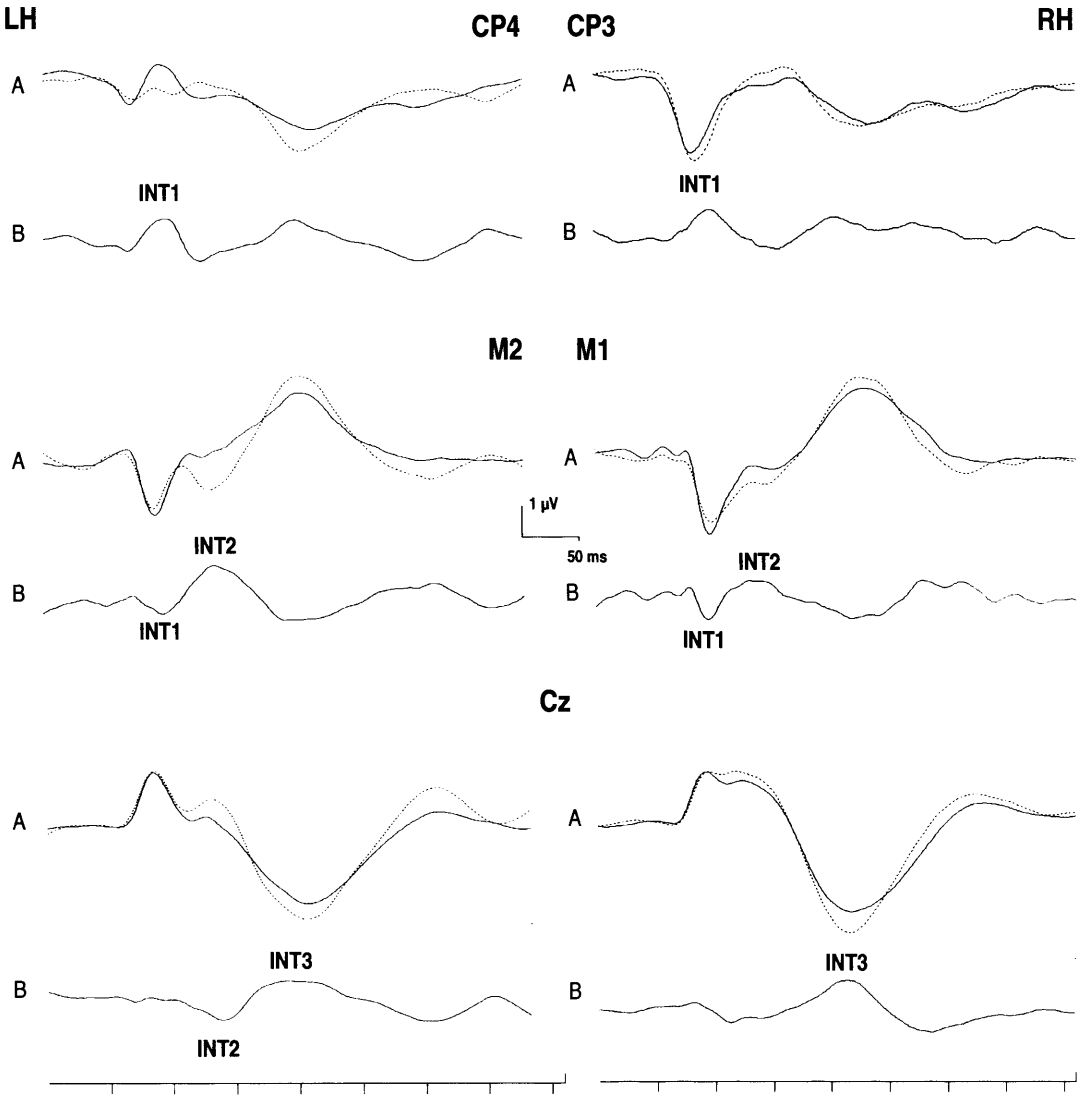


Figure 8.2: Grand average responses at representative electrodes depicting the interactions, INT1, INT2, and INT3, between auditory and somatosensory responses for the two groups, group 1 (RH) and group 2 (LH). Trace A is the AS response (dashed line) overlying the D response (solid line). Trace B is the corresponding subtraction waveform. Waveforms have been filtered with 40Hz highpass filter, 12dB/oct. Note that INT1 was only seen unilaterally.

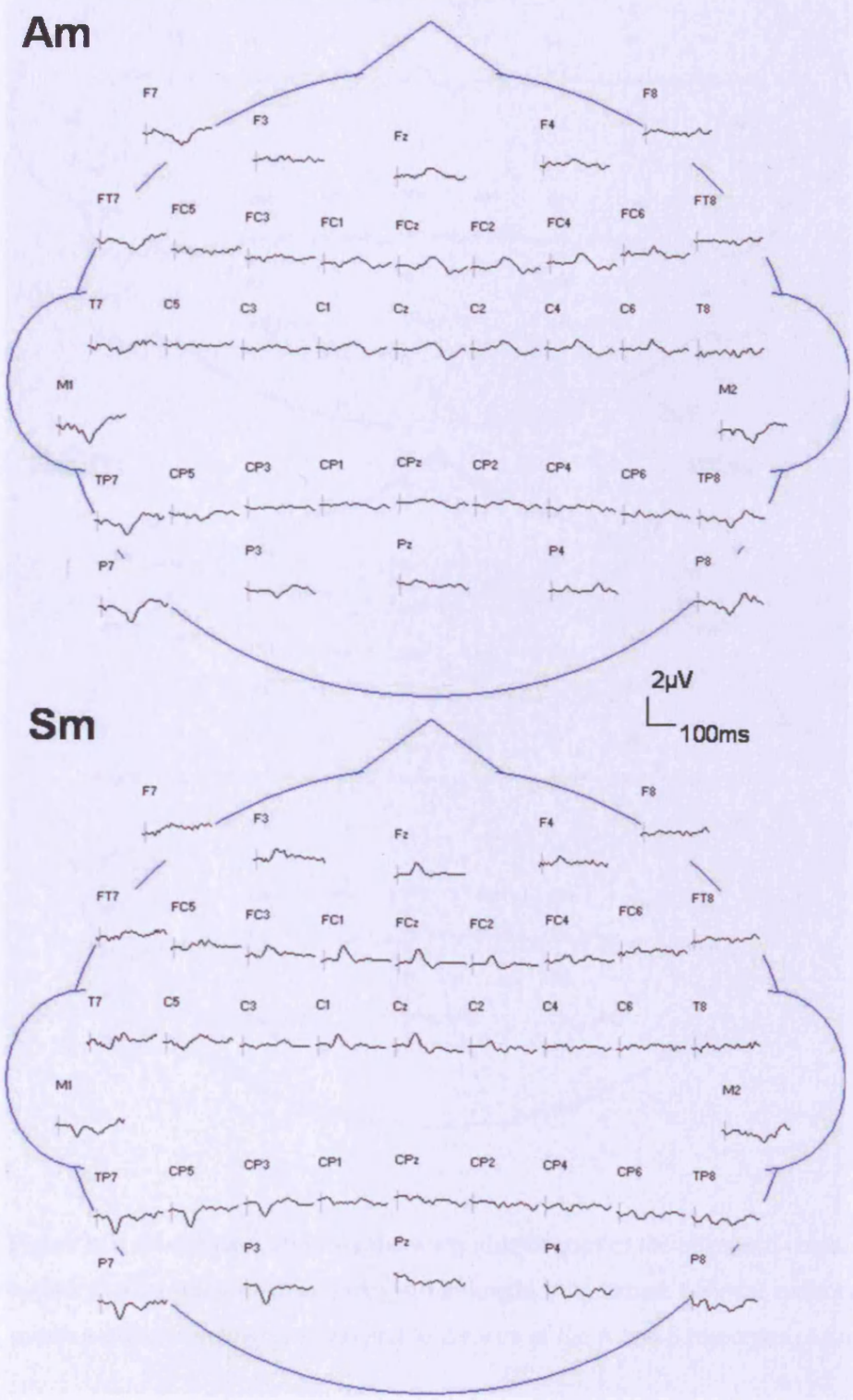
8.5.2 ASm vs. Dm - mismatch responses

8.5.2.1 Mismatch responses to auditory, somatosensory and dual stimulation

Mismatch responses for each of the stimulus conditions were obtained by subtracting the responses to the pre-deviant standard stimuli from those of the deviant stimuli. The distribution and timing of the unimodal responses were typical of those previously reported for mismatch responses (fig. 8.3).
The ASm was calculated by summating the unimodal sMMR and aMMN responses. The amplitude of the main negative peak between 100-150ms of the Dm and ASm responses (at Cz) was compared to the prestimulus noise level. In all subjects, of both groups, the Dm response exceeded statistically the pre-stimulus noise level ($p<0.05$). This was also the case in 14 out of 16 subjects in Group 1, and 9 out of 10 subjects Group 2, for the ASm responses. T-tests on the mean amplitude of ASm and Dm for both groups at Cz, M1 and M2 were significant ($p<0.001$).

When the Dm response is compared with ASm response (Fig. 8.4) there is a clear difference between the traces indicating the existence of an audiotactile interaction within the discrimination process. After right-sided stimulation these interactions were largest around 145ms over the midline fronto-central region and around 215ms over the left frontal region. After left-sided stimulation the corresponding responses peaked around 143ms over the midline fronto-central areas and around 207ms over the left frontal region. The mean amplitudes of the ASm and Dm responses were statistically compared using two-way repeated measures ANOVA, with factors of stimulus type (ASm and Dm) and electrode (C1, C2, Cz, FC1, FC2, FCz, F3, F4, F7,F8, Fz) over the 60ms time windows around the latency of the peak in the grand average responses. The Dm responses

were shown to differ significantly from the ASm responses in both Group 1 (115-175ms: $F(1,10)=30.85$, $p< 0.001$; 185-245ms: $F(1,10)=6.63$, $p<0.012$) and Group 2 (115-175ms: $F(1,10)=41.07$, $p< 0.001$; 177-237ms: $F(1,10)=14.48$, $p< 0.001$).



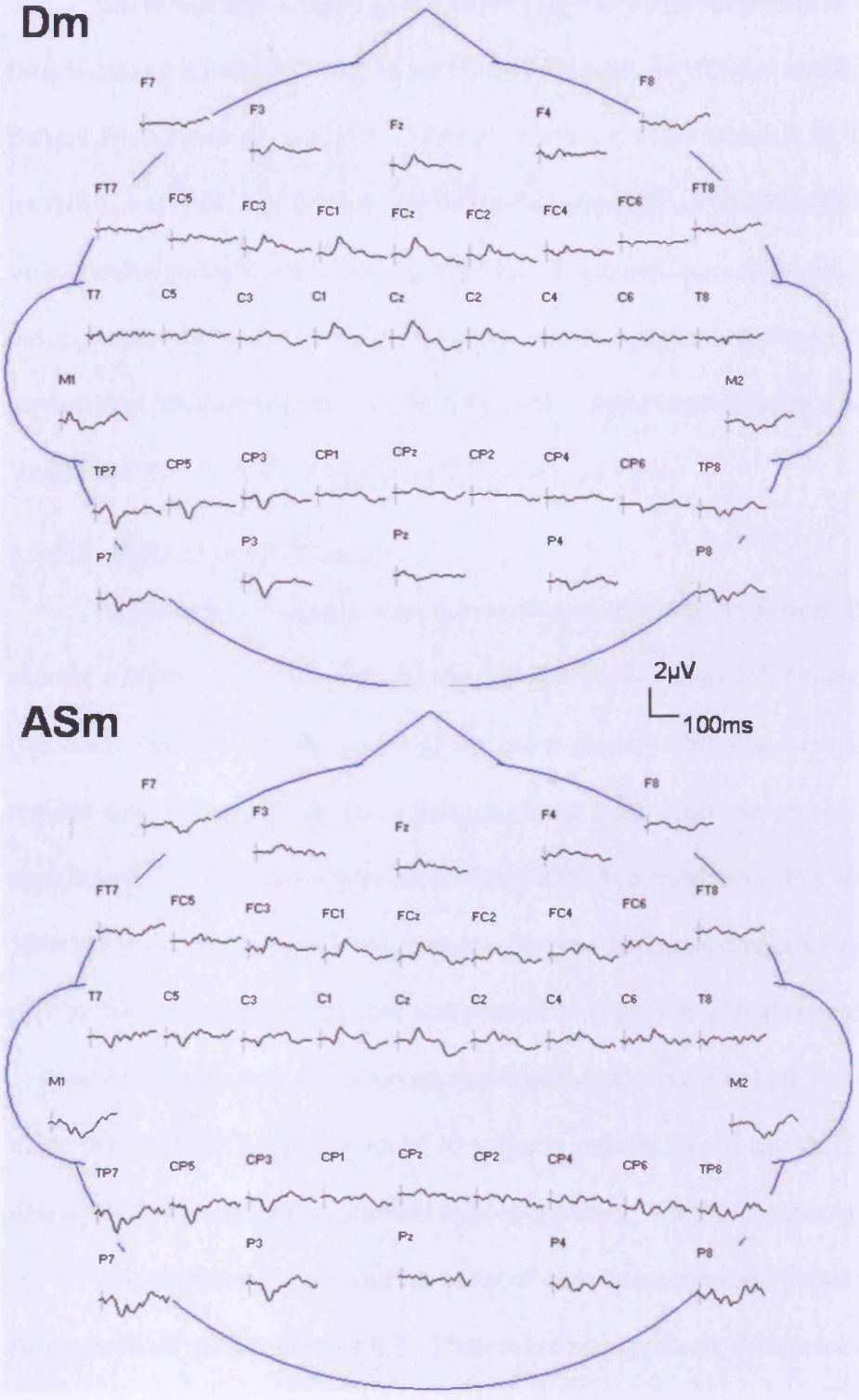


Figure 8.3: A schematic showing the scalp distributions of the mismatch responses to auditory (Am) and somatosensory (Sm) unimodal stimulation, bimodal auditory and somatosensory stimulation (Dm) and to the sum of the A and S responses (ASm).

There was also a significant stimulus type by electrode interaction for both time windows (Group 1: 115-175ms: $F(10,165)=5.86$, $p< 0.001$, $\varepsilon =0.001$; 185-245ms: $F(10,99)=8.17$, $p<0.001$, $\varepsilon =0.001$. Group 2: 115-175ms: $F(10.99)=3.84$, $p< 0.001$, $\varepsilon =0.001$; 177-237ms: $F(10,99)=2.04$, $p<0.037$, $\varepsilon =0.037$). In the first time window posthoc analysis showed a significant difference between the F8/F4 electrodes and the other electrodes ($p<0.05$) but no difference between them. In the second time window post hoc analysis showed a significant difference between the frontal and the other electrodes ($p<0.05$) in both groups.

8.5.2.2 Subtraction waveform

A difference waveform was obtained by subtracting ASm from Dm and showed a biphasic interaction response with two components INT1m and INT2m (fig. 8.4). The INT1m component peaked over the mid central and fronto-central regions and in 14 out of the 16 subjects in Group 1 this response exceeded significantly the pre-stimulus noise level ($p<0.05$, binomial test). In Group 2, all 10 subjects showed a significant response, but one had opposing polarity. The INT2m component appeared later and peaked over the left frontal region. In Group 1, 9 out of 16 subjects had responses that significantly exceeded the pre-stimulus noise level and in Group 2, 9 out of 10 subjects showed significant INT2m responses (the same subject showed opposing polarity for this component as well).

The peak amplitudes and latencies of each interaction component for the two groups are shown in table 8.2. There were no significant differences in the amplitude or latency of INT1m between the central/fronto-central electrodes for either group. INT2m appeared over the left fronto-central region with a significantly higher peak amplitude recorded from F7 for both Group 1 ($F(5)=70.55$, $p<0.001$) and Group 2 ($F(5)=45.65$, $p<0.001$). There were no

There was also a significant stimulus type by electrode interaction for both time windows (Group 1: 115-175ms: $F(10,165)=5.86$, $p< 0.001$, $\varepsilon =0.001$; 185-245ms: $F(10,99)=8.17$, $p<0.001$, $\varepsilon =0.001$. Group 2: 115-175ms: $F(10.99)=3.84$, $p< 0.001$, $\varepsilon =0.001$; 177-237ms: $F(10,99)=2.04$, $p<0.037$, $\varepsilon =0.037$). In the first time window posthoc analysis showed a significant difference between the F8/F4 electrodes and the other electrodes ($p<0.05$) but no difference between them. In the second time window post hoc analysis showed a significant difference between the frontal and the other electrodes ($p<0.05$) in both groups.

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significant differences in the latency or amplitude of either component between the two groups.

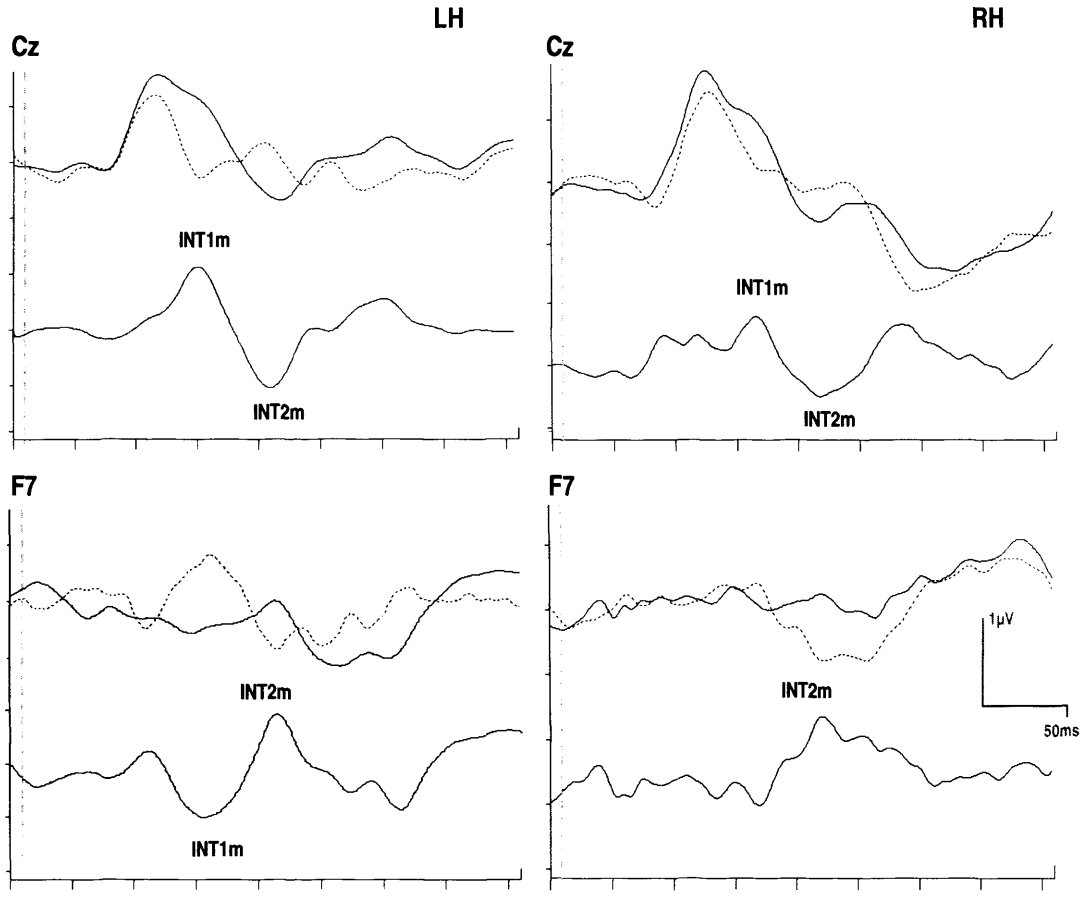

Figure 8.4: Grand average responses at representative electrodes depicting the interactions, INT1m and INT2m, between auditory and somatosensory mismatch responses for the two groups; group 1 (RH) and group 2 (LH). The upper trace is the ASm response (dashed line) overlying the Dm response (solid line). The lower trace is the corresponding subtraction waveform. Waveforms have been filtered with 40Hz highpass filter, 12dB/oct.

	Group 1		Group 2	
Comp	**Lat (ms) ±SD**	**Amp (μV) ±SD**	**Lat (ms) ±SD**	**Amp(μV) ±SD**
INT1m	148.8 ±23.4	-2.32 ±1.17	140.4 ±18.0	-1.77±0.85
INT2m	218 ±15.3	-2.95 ±1.22	207.4 ±9.39	-2.24 ±0.91

Table 8.2: Peak latency and amplitude values for each interaction components observed in the Dm-ASm subtraction waveform.

8.5.3 Subjective Perceptions of the Participants

All subjects perceived the auditory and somatosensory as belonging together, but also found them easy to ignore once the distraction task had begun. When asked about the relative intensities of the two stimuli, a large number of the subjects (11 out of 25) were uncertain which was more intense, with 9 reporting the tactile stimulation as having greater salience and 5 reporting the auditory as such.

8.6 Discussion

The present study examined the interaction effects between the responses to standard auditory and tactile stimuli and between auditory and somatosensory mismatch responses. Analysis of the standard responses revealed three main phenomena, a parietal effect at 65-95ms, a temporo-parietal effect at 120-140ms and one in the centro-parietal region at 190-220ms, which are consistent with previous literature. The mismatch responses also revealed interaction effects occurring over the vertex at 135-150ms and left fronto-central regions at 190-220ms. There was no evidence of an anticipatory slow wave.

8.6.1 Interactions between somatosensory and auditory ERPs to standard audiotactile stimulation

The early interaction response, INT1, has a latency and distribution consistent with the early components reported in previous studies and it has been proposed that this interaction occurs in either the contralateral SI (Foxe et al., 2000), the contralateral auditory association cortices (Murray et al., 2005) or the posterior parietal cortex (PPC) (Gobbelé et al., 2003). However the evidence for a SI generator is based on the early timing of the interaction effect and on evidence of visual-tactile interactions reported in the monkey SI cortex (Zhou and Fuster,

1997), which led to the hypothesis of multimodal integration in the human SI. Support for a generator located in the PPC is slightly more convincing. Monkey studies have shown audiotactile interactions within the ventral intraparietal sulcus (Lewis and Van Essen, 2000) and fMRI data suggests that the human homologue of the monkey VIP is located in the PPC (Bremmer et al., 2001). Source analysis on the early audiotactile interaction performed by Gobbelé et al. (2003) indicated a PPC generator; however discrepancies between the left and right hemisphere responses suggest that a SI generator cannot be ruled out. The early interaction reported by Murray et al. (2005) occurs earlier than those of the other studies and may reflect a different process.

Interaction effects with latencies and topographies consistent with INT2 have been reported by Gobbelé et al. (2003) and Lütkenhöner et al., (2002). A second interaction effect with similar topography was also reported by Foxe et al. (2000) but it had a considerably earlier peak latency (80ms vs. 130ms). The most common consensus is that this interaction arises in the SII cortex, but contributions from the auditory cortices cannot be ruled out. Involvement of the auditory cortices would be more in keeping with the scalp distribution of the INT2 component found in this study. In this study the INT 2 component showed a clear phase reversal between the M1/M2 and Cz, which was more anterior and lateral to that of the P100 component, which is generally held to originate in SII.

Only Lütkenhöner et al., (2002) has reported an interaction effect with the same general latency and topographical distribution to INT3. They proposed that this component is also generated in the SII cortex. This would be consistent with the scalp distribution of the INT3 component.

8.6.2 Interactions between sMMR and aMMN responses to audiotactile stimulation

The mismatch negative response to deviance on both the auditory and somatosensory dimension in a bimodal event includes both supratemporal and parietal components that were consistent with the unimodal mismatch responses. This suggests that the deviance detection processes operate separately to a certain extent. However comparison of the dual mismatch response with the sum of the unimodal mismatch responses reveals a biphasic interaction effect. The earlier component, INT1m, appears maximally over the vertex and the later component, INT2m, appears maximally over F7 with a clear phase reversal over the left fronto-central region. The scalp distribution of INT1m would be consistent with an SII generator; however other regions cannot be excluded. The scalp distribution of INT2m suggests cortical origins within the left prefrontal region. As discussed in chapter 6, the dorsolateral prefrontal cortex (DLPFC) and MFG have been implicated in a multimodal parietal-frontal network involved in selective attention and sensory memory processing. The DLPFC has also been shown to play a role in biasing and prioritising sensory information (Assaf, et al., 2006; Milham et al., 2003) and interactions between the auditory and somatosensory discrimination response may reflect some of the electrical activity underlying these processes. Unfortunately one of the limitations of the technique used in this study is that it is unable to ascertain whether the effects seen at the scalp surface represent inhibitory or excitatory interactions.

8.7 Conclusions

The interaction effects between auditory and somatosensory stimuli reported in this study are in good agreement with those reported previously and

thus confirm the efficacy of the technique in eliciting interaction responses. The hypothesis of completely independent auditory and somatosensory discrimination processes is unlikely as this study has shown interaction effects between these two processes at an early stage. Further study may focus on the relationship between the MMN interactions and biasing/prioritising processes, and on the effects selective attention and stimulus salience may have on these interactions.

Chapter 9: Discussion and Conclusions

Underpinning our highest intellectual ideas and our most creative thoughts are the basic impressions of the environment received through our primary senses. The sense of touch is the most diverse of these senses and the experiments in this thesis were designed to look at one small part; the early, pre-attentive processing of stimulus change using event-related potentials in response to vibrotactile stimulation to the fingertips.

9.1 Methods used in the thesis

Most of the experimental methods used in this thesis were chosen because either there is a large body of literature showing them to be appropriate and reliable for studying mismatch responses, such as the odd-ball paradigm (section 2.1.4.1), or they were an attempt to minimize the effects of certain variables. Those in the latter category include vibrotactile stimulation, immobilization with a vacuum cast and dynamic force monitoring.

The use of vibrotactile stimuli allowed for a greater flexibility in manipulating the stimuli than is possible with electrical stimulation (section 2.2.3). The use of higher frequency vibration (>60Hz), selectively stimulated mainly one type of mechanoreceptor (Pacinian receptors) and associated nerve pathway (sections 1.2.1 and 2.2.3.1) as opposed to global median nerve stimulation. This more specific stimulation helps to minimize possible confounding effects on the SERP resulting from mass stimulation.

The forearm, wrist and part of the hand of the adult subjects were immobilized in a vacuum cast (section 4.3.3.3). This was used to suppress movement of these regions. By suppressing movement, extraneous receptor and

cortical activations were minimized. Immobilization should also help to control the variations in the intensity of the vibration stimulus being applied to the fingertips, which may result from movements and associated pressure variations. (section 4.3.1).

Despite the vacuum cast, it was not possible to completely eliminate movement of the fingers and hands. In addition, the weight of the individual subjects' hands may vary considerably. Both of these factors result in variations in the load on the vibratory stimulator, which in turn causes variations in the intensity (or dynamic force) of the stimulus being applied to the fingertips. Therefore the dynamic force of the stimulus being applied throughout each trial was monitored and the experiment described in section 4.3 was performed to prove that these small variations in stimulus intensity would not significantly alter the resulting ERPs.

9.2 Mid/late somatosensory ERPs

The studies reported in chapter 5 explored the effect of stimulus duration on mid to long latency SERPs and characterized a number of novel components.

9.2.1 *On-* and *off-* responses in the somatosensory system

The two studies in chapter 5 revealed clear *on-* and *off*-responses to a range of stimulus durations. These had previously been reported for the visual and auditory systems, but were a novel finding for the somatosensory system (section 5.1).

The somatosensory *on*-response consists of the N35-P50/P100 complex and these have been studied extensively in the past. In addition to these, two later components were also observed; a small positive deflection (Po1) followed by a

larger negative deflection (No1). These had not been previously reported, and had a timing consistent with the offset of the stimulus, i.e. they consistently appeared at the same latency following the cessation of the stimulus (on average at 85 and 130ms respectively) regardless of the duration of the stimulus (section 5.4.1). The Po1 component of the responses to stimulus durations under 150ms was not readily detectable and is thought to be embedded within other components, such as the P100 or N140, in a manner similar to the short duration off-set responses observed in the auditory system (see section 5.1.1.1 for review). The No1 component of the *off*-response is larger and easier to measure at shorter durations. It increases in latency as the stimulus duration increases but appears consistently around 130ms following the cessation of the stimulus. The distribution of the *off*- response is very similar to that of the *on*- response, appearing maximally over the contra-lateral parietal region, with phase reversal over the central-parietal areas (section 5.4.1).

Similar to results obtained from auditory stimulation (Hillyard and Picton, 1978), the amplitude of the *on*-response decreased with increasing stimulus duration with no change in the *off*-response. This interaction between the two responses suggests that they are not physiologically independent processes. Evidence from auditory source analysis (Noda et al., 1998, Pantev et al., 1996) and somatosensory cellular recordings support this premise (Sur et al., 1984).

The *on*-response is a complex of the P50 and P100 components, often with a more pronounced P100. These components are thought to arise from SI and SII cortices respectively (Hämäläinen et al., 1990) and it is probable that the *off*-response is similarly a complex of components reflecting activation of different cortical areas. The contra-lateral emphasis of these responses may reflect the contribution of the lateralized P50 (SI) responses and more precise stimulation may

be able to separate the P50 and P100 responses and there may even be a difference between SI and SII *on*- and *off*–responses. Further study may reveal similar processes taking place in higher order somatosensory areas such as Brodmann area 40.

9.2.2 The *sustained*-potential

A *sustained*-potential was observed to follow the P100 component and the waveform would approach, but not reach, the baseline before the *off*-response appeared. Again, a similar component, the *sustained*-field response, has been reported in the auditory and visual systems (Crevits et al., 1982; Hari et al., 1997; Picton et al., 1978b) but it is a novel finding in the somatosensory system. Studies in the auditory system have shown it to be distinct from the CNV (Picton et al. 1978b). In the studies reported in chapter 5, the onset of the *sustained*-potential was earlier than the latencies reported for the CNV (>400ms) (Rebert and Knott, 1970) and it was recorded in both the attended and unattended conditions, making it unlikely to be the CNV.

The distribution of the *sustained*- (somatosensory) potential is lateral and anterior to that of the *on*- and *off*- responses, but like the *on*- and *off*- responses it has a contralateral emphasis. The difference in distribution suggests that the cortical generators may arise in an area separate from the SI or SII regions. Animal studies have found a group of slowly adapting neurons that respond throughout the duration of the stimulus and have a slightly different distribution from those cells responding only to stimulus onset or offset (Sur et al., 1984).

9.2.3 Somatosensory ERPs to attended stimuli

Attending to the somatosensory stimuli was found to enhance the amplitude of the transient and sustained responses. The increase in the amplitude of the sustained response may reflect an actual increase in the sensory *sustained–* potential, however the possibility of an added CNV associated with temporal uncertainty can't be ruled out. The increase in amplitude and decrease in latency of the transient *on-* and *off* –responses are similar to those reported for other sensory modalities.

9.2.4 Summary

The SERP components described above have analogous responses in the auditory and visual systems. The general similarity between these late evoked potential responses in the primary sensory cortices may reflect a common basis that enables further cognitive processing and sensory integration. Characterization of these responses will allow one to predicate how they may change or interact within the manipulation of somatosensory stimuli and subsequent cognitive processing. For example, one of the effects of increasing stimulus duration was a significant alteration in waveform morphology (as a result of the *sustained*-response) at relatively small duration differences. This had to be accounted for when devising the experimental set-up that used different duration stimuli.

9.3 The somatosensory mismatch response

The purpose of the experiments performed in chapter 6 was to determine the effects of changes in the duration or frequency on the somatosensory discrimination response. The intracranial studies in chapter 7 expanded on the results obtained in chapter 6 and results of the child control study suggest there are

no large differences between children and adults that would compromise the extension of the intracranial results to adults.

9.3.1 sMMR components and distribution

A change in either the duration or the frequency of vibratory stimuli presented using an unattended odd-ball paradigm elicited a biphasic shift that was only observed in the deviant SERP. A subtraction waveform obtained by subtracting the response to the pre-deviant standard stimuli from the deviant response revealed a biphasic response (MN1-MP1) with a centro-parietal distribution on the scalp and maximum amplitude over the post-central gyrus in the intracranial recordings. This suggests a generator in SI, as proposed previously (Kekoni et al., 1997), and would be in keeping with a recent fMRI study by Preuschhof et al. (2006), which also implicated the human SI in the encoding process of vibrotactile, working memory.

In addition to the MN1 and MP1 components, the intracranial recordings revealed a second negative component (antMN1), which appeared maximally over the left middle frontal gyrus. This component is of considerably lower amplitude than those recorded over the parietal region. No reliable antMN1 responses were observed in the scalp recordings, most likely due to the small amplitude of these responses.

9.3.2 The MP1 component

Scalp and intracranial recordings have consistently shown that the MP1 component was not present in stimulus conditions where the deviant stimulus was of a shorter duration than the preceding standard, suggesting that the order of stimulus presentation may have a greater impact on the MP1 component than on

the MN1. Similarly, a positive component following the negative one was also reported by Akatsuka, et al. (2005) in a study using a two-point discrimination method to examine somatosensory mismatch processing. They held that the loss of the positive component reflected differences in the threshold for detecting paired stimuli vs. unpaired stimuli, however it is more likely this negative shift in the positive component is due to changes in the temporal characteristics of the stimuli, particularly the duration (for discussion see chapter 6). These results suggest that the stimulus duration and order of presentation has an effect on the MP1 component and therefore need to be considered when studying the sMMR particularly when examining changes in the temporal characteristics of stimuli.

The MP1 shows a different topography and differing sensitivity to the order of presentation of different duration stimuli than the MN1, thus implying that it may have a different cortical generator. Such a generator may lie within the ventral premotor cortex. This area has been shown to be involved in the processing of temporal patterns, independent of modality, (Schubotz et al., 2003; Schubotz and von Cramon, 2001) and in frequency processing of vibrotactile stimuli (Preuschhof et al., 2006). Other possible locations have been implicated in vibrotactile discrimination lie within SII (Preuschhof et al., 2006) or the pre-central gyrus (Kekoni et al., 1997).

9.3.3 Discrimination responses to Frequency and Duration deviants

Comparison of the topography of the frequency elicited sMMR and duration elicited sMMR was made in two intracranial subjects and clear differences were in the topography of the two responses were observed. The frequency sMMR appeared closely adjacent to, but more posterior than, the duration sMMR. Similar findings have been reported from intracranial studies examining the aMMN (Liasis

et al., 2000). The peak latencies of both the MN1 and MP1 components were influenced by the duration of the stimulus, with longer duration stimuli eliciting longer latencies, in a manner similar to that of the aMMN (Jaramillo, 2000). Several studies have reported a clear fronto-central negative shift in response to an infrequent change in a stream of stimuli, but there have been discrepancies in the latency of this response (see section 3.4). The results from experiment 6 (section 6.5) suggest that the dependency of the latency of MN1 component on the duration of the stimulus may account for these discrepancies. The studies from the literature reporting an enhanced N60 component used brief 0.1-0.2ms electrical stimulation while experiment 6 of this thesis and Kekoni et al. (1997) used longer vibration stimuli (300ms) and observed peak latency values ranging between 100-200ms. Therefore the latency differences in the responses to the vibration stimuli versus those of the electrical stimuli may be a result of the duration of the stimulus used, with longer duration stimuli resulting in increased peak latencies.

9.3.4 The somatosensory discrimination response as a reflection of haptic memory

Auditory mismatch processing is thought to be an encoding process within the brain that reflects echoic memory (section 3.2). Section 3.1.1 outlines a number of characteristics defining a mismatch process. If the somatosensory mismatch response is to be considered a homologue of the aMMN and thus reflect haptic memory, it must be shown to have these same characteristics.

The first characteristic is that mismatch processing is not simply the response of different neuronal populations responding to new afferent elements of the deviant stimulus but is generated by encoding processes within the brain. As the frequency deviant stimuli used by Kekoni et al. (1997) (section 3.4.1) were

similar to those used in this study, it seemed unnecessary to repeat these experiments. However Kekoni et al. (1997) also reported that the late ERPs recorded in the standards-omitted paradigm were similar to the corresponding response to the first stimulus in a stimulus train paradigm. Thus, as a control measure, the first standard response in each run was averaged and compared to the corresponding average of the first deviant responses. The first standard response averages showed the same enhancement in the amplitudes of the P50, P100, and N140 components as the first deviant averages. This is compatible with the results reported in the standards-omitted paradigms of the previous studies and reflects a rate effect, where unspecific components habituate (section 2.1.2.1). Comparison of the standard N140 component to the corresponding deviant MN1 response in each of the stimulus conditions showed a significant difference in distribution, with the MN1 component appearing more lateralized.

Another characteristic of mismatch processing is that it is pre-attentive. This is demonstrated in this thesis by the successful recording of the sMMRs using experiments in which the subjects were required not to attend the stimuli and were distracted either by watching a video or by performing a visual matching task (chapters 6, 7 and 8). This is further supported by the lack of P300 SERP component (section 2.2.1.2), which if present, would signal attention processing.

The mismatch process is also independent of stimulus feature and is a reflection of the behavioural discrimination threshold. The results of experiments 6 and 7 and the discrimination task described in chapter 6 (section 6.5) demonstrated the somatosensory MN1 potentials were very similar in morphology and latency, regardless of whether the deviant was a frequency or duration change. In addition to this, subjects found the longest stimulus pair, 170/250ms, particularly difficult to

discriminate, being close to the behavioural discrimination threshold, and the SERP results reflected this, with the MN1 and MP1 components being significantly lower in amplitude or absent.

Based on the above results and those previously published in the literature (see section 3.4.1 for review) it is reasonable to infer that the sMMR is a mismatch process and that it is an electrophysiological index of change, with the amplitude being related to a sensory discrimination process analogous to the aMMN.

9.4 Multisensory interactions

The experiments performed in chapter 8 examined possible interactions in the ERPs between temporally and spatially concordant audio tones and vibrotactile stimuli. Interaction effects between standard auditory and somatosensory responses and between auditory and somatosensory mismatch responses were observed.

9.4.1 Interactions between somatosensory and auditory ERPs to standard audiotactile stimulation

Analysis of the standard responses revealed three main interaction effects; one with a parietal distribution (INT1), one with a temporo-parietal distribution (INT2) and one with a centro-parietal distribution (INT3). The latency and topography of these components are consistent with those previously reported (Foxe et al., 2000; Foxe et al., 2002; Gobbelé et al., 2003; Lütkenhöner et al., 2002). The cortical locations of these interactions are still uncertain. Generators within SI (Foxe et al., 2000) or the PPC (Gobbelé et al., 2003) have been proposed for first early interaction, with a stronger case being put forward for the PPC (see

chapter 8 for discussion). Origins within SII and/or the auditory cortices have been proposed for the second component (Gobbelé et al., 2003; Lütkenhöner et al., 2002). The distribution of INT2 would support involvement of the auditory cortices. The distribution of INT3 suggests possible origins within SII, which is in keeping with similar findings reported by Lütkenhöner et al. (2002).

9.4.2 Interactions between sMMR and aMMN responses to audiotactile stimulation

Interactions between auditory and somatosensory discrimination processing was also observed. Comparison of the bimodal mismatch response with the sum of the unimodal mismatch responses reveals a biphasic interaction effect (INT1m/INT2m). The INT1m effect has a central distribution, which may suggest an SII generator, while the later INT2m effect has a fronto-central distribution, suggesting a generator within the prefrontal cortex. The dorsolateral prefrontal cortex and MFG have been implicated in a multimodal parietal-frontal network involved in selective attention and sensory memory processing.

9.5 Memory processing and the sMMR

9.5.1 A parietal-frontal network

Previous ERP, MEG and fMRI studies have demonstrated that oddball paradigms, such as those used to study the MMN, evoke widely distributed activity in cortical and subcortical neuronal networks, usually associated with the P300 (McCarthy and Wood, 1987; Wang et al., 2003) and a number suggest that, in addition to sensory specific cortical generators, there is a modality independent frontal – parietal network that is commonly activated during auditory, visual and somatosensory oddball tasks (Ardekani et al, 2002; Huang et al., 2005; Linden et

al., 1999; McCarthy et al., 1997). Fronto-parietal networks are thought to be prominently involved in the encoding, storage and executive functions, such as selective attention (Milham et al., 2003; Huettel and McCarthy, 2004; Preuschhof et al., 2006). These networks contain modality specific regions, which include SI and SII for somatosensory stimulation and modality independent regions, which include the inferior parietal lobule (IPL)/supramarginal gyrus (SMG), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and middle frontal gyrus (MFG).

Sensory memory is thought to be a 'buffer' for working memory, with selective attention mechanisms directing what information is encoded. The sMMR is thought to reflect haptic memory processes, and the temporal and spatial characteristics of the responses are consistent with components of the somatosensory fronto-parietal network (Huang et al., 2005) and thus may reflect activity within this network. The interactions between the aMMN and sMMR may be a measure of crossmodal biasing effects on the selective attention processes.

9.5.2 Anterior mismatch responses and memory processing

The anterior components of the aMMN and sMMR have both been shown to have similar latencies and to have their origins in the DLPFC and the MFG. These topographical and temporal similarities support the premise that they may reflect the activity of modality independent regions of the parietal-frontal network activity.

The DLPFC and MFG have been shown to be involved in a number of storage and executive processes, including the formulation of response strategies (Preuschhof et al., 2006; Huettel and McCarthy, 2004), biasing the processing of the contents of working memory (Milham et al., 2003) and in the encoding and

maintaining of vibrotactile memory traces (Preuschhof et al., 2006); however the predominance of function in these two regions appear to involve focusing attention on relevant information and processes and inhibiting irrelevant ones (Hartley and Speer, 2000). One of the interaction effects between the aMMN and sMMR was seen to be similarly distributed over the left pre-frontal cortex and this interaction may specifically reflect these cortical mechanisms. Thus one can speculate that the interaction effects recorded between the sensory modalities may be used to quantify biasing processes that underlie the encoding, maintenance and decision making mechanism of working memory.

9.6 Cortical theories of mismatch responses

At the cognitive level, mismatch responses are thought to be the consequence of change-sensitive processes that reflect the automatic detection of sensory change and pre-attentive processing. Mismatch responses may correlate with involuntary attention switches and engage memory systems (Näätänen, 2003). However this does not explain the mechanics of the mismatch responses at the neuronal level, which is currently an area of theoretical interest. There are two main hypotheses concerning the genesis of the aMMN that may be expanded to include mismatch responses in the other sensory modalities. These are the 'intrinsic adaptation' and 'predictive coding' hypothesis.

9.6.1 The intrinsic adaptation hypothesis

The intrinsic adaptation hypothesis proposes that the preceding standard stimuli of the odd-ball paradigm will adapt feature-specific neurons via local connectivity. In the auditory system, this view proposes that the N1 auditory response comprises of an anterior and posterior component that are differentially

adapted by the preceding auditory stimuli. The posterior component is suppressed and delayed on repeated exposure to the standard stimulus and this results in a difference between the standard and the deviant responses that corresponds to the aMMN (May et al., 1999; Jääskeläinen et al., 2004).

Experimental results combined with computational modelling provide some support for this theory (May et al., 1999; Jääskeläinen et al., 2004) and recent dynamic causal modelling of the aMMN performed by Kiebel et al. (2007) show a good fit with models based on simple local adaptation. However this theory is unable to account for a number of findings. It cannot explain the presence of the mismatch response in experimental paradigms where the deviant stimulus is not a change in stimulus feature. For example, the aMMN response is evoked when there is a missing, but expected, tone and when there is a violation in some predictable feature pattern (i.e. a tone ladder) (Näätänen et al., 2005). Intrinsic connectivity alone cannot explain lesion studies that suggest prefrontal effects on the temporal aMMN, where patients with prefrontal lesions exhibit diminished temporal aMMN (Alain et al., 1998). Finally the adaptation hypothesis cannot easily explain the inverse relationship between aMMN amplitude and the deviant probability (Javitt et al., 1998; Winkler et al., 1996).

If this theory is applied to the sMMN then it is feasible that the N140 component could be the somatosensory analogy of the N1. Like the N1, the N140 is thought to have multiple generators. This being the case, then the sMMN described in this thesis could conceivably be the result of differential adaptation of feature specific neuronal populations that contribute to the N140 response. However this theory cannot easily explain the interaction effects between auditory and somatosensory mismatch responses reported in chapter 8.

9.6.2 The predictive coding hypothesis

The predictive coding hypothesis is based on the assumption that the brain infers the causes of its sensory inputs by predicting them and adjusts these predictions in order to minimize error, which then leads to perceptual learning. This minimization of prediction error is thought to rely on a hierarchical network operating on an empirical Bayes scheme with extrinsic (forward and backward connections between cortical sources) and intrinsic (local) connectivity (Friston, 2005). Thus, with respect to mismatch responses, this view proposes that the sensory input entering the primary sensory cortex is dynamically compared with top-down predictions. Differences between the generative predictive model and the sensory input results in a prediction error, which is then passed to the next level in the hierarchy where the prediction is adjusted and sent back down to try and account for the prediction error. The mismatch response is thought to represent a failure to suppress prediction error. In the auditory system, it has been proposed that a component of the N1 response corresponds to prediction error that is rapidly suppressed with repeated exposure to the standard stimuli via top-down predictions (Kiebel et al, 2007; Friston, 2005). When the stimulus is rare or unpredictable, the minimization of prediction error takes longer and hence the emergence of the aMMN.

A growing body of theoretical and empirical evidence supports predictive coding as a parsimonious explanation not only for mismatch responses, but for a range of other phenomena (Kiebel et al., 2007; Friston, 2005; Baldeweg et al., 2004; Rao and Ballard, 1999). The aMMN framework also provides a coherent explanation for disconnectivity disorders such dyslexia and schizophrenia (Stephan et al., 2006; Friston, 2005). However recent dynamic causal modelling of the

aMMN for the predictive coding hypothesis done by Kiebel et al. (2007) has shown no better fit for the combined extrinsic/intrinsic connectivity of this hypothesis than for the pure intrinsic connectivity of the adaptation hypothesis and they showed worse fit for models using only extrinsic connections.

If it is assumed that the modelling work done on the aMMN holds true for other mismatch responses, then the sMMN can be explained in a manner similar to the aMMN with components of the N140 reflecting prediction error. In addition to these mismatch responses having sources originating within the sensory cortices, later anterior mismatch responses are also found with frontal sources that may reflect predictive coding occurring at a 'higher' cortical level. The interactions between the aMMN and sMMN reported in chapter eight had scalp distributions compatible with anterior sources and may reflect activity of multimodal cortical areas. In this case, the mismatch responses suggesting interactions showed slight attenuation of the aMMN component. Thus, based on a predictive coding model, one possibility is that intrinsic connections, which have been shown to be important in generating mismatch responses (Kiebel et al., 2007), cause an inhibitory interaction on the auditory inputs. This in turn would affect the forward extrinsic connectivity of this information to a higher cortical level and subsequently would affect prediction error resolution and eventual perceptual learning of the auditory information. This would be compatible with the subjective experience of many of the subjects who reported the tactile stimulus as the more salient. Thus these interactions may reflect a gating mechanism for different types of sensory input.

9.7 Conclusions

The results of the experiments performed in this thesis lend themselves to the following conclusions.

1. *On*-set, *off*-set and *sustained*- responses may be seen in response to vibrotactile stimuli. These are consistent with responses reported in the visual and auditory system, but in contrast with these other sensory modalities, they begin to be observed at quite short stimulus durations (<100ms).

2. There is a somatosensory discrimination response, which appears analogous to the auditory mismatch negativity. It consists of three components; two negative (MN1, antMN1) and one positive (MP1). MN1 appears maximally over the post-central gyrus and antMN1 appears later over the middle frontal gyrus. MP1 occurs later than the negative components and is located near the MN1 component.

3. The sMMR can be elicited by either frequency or duration stimuli. The latency of the sMMR is sensitive to the duration of the stimuli, with longer durations increasing the latency. Frequency and duration evoked sMMR may have different cortical generators, which lie closely adjacent in the post-central gyrus.

4. The standard responses to bimodal audio tones and vibrotactile stimulation are significantly different from the arithmetic sum of the unimodal responses, suggesting that auditory and somatosensory processing are not independent processes. The areas of variation indicate interactions between the two modalities. Three areas of interaction were observed, an early one with a contralateral centro-parietal distribution, one with a bilateral temporo-parietal distribution and a later one with a bilateral centro-parietal distribution.

5. Mismatch responses to bimodal audio tones and vibrotactile stimulation are significantly different from the arithmetic sum of the unimodal mismatch responses. This suggests that auditory and somatosensory discrimination processing are not independent processes and that the regions of variation indicate interaction between the two modalities. Two interaction effects are observed, one with a bilateral central distribution that was followed by a second one with a left fronto-central distribution, which was independent of the side of stimulation.

9.8 Future Directions

The results of the experiments in this thesis open a number of avenues to be explored. The most topical at the moment would be further examination of the interactions between the different sensory modalities during multisensory stimulation. It would be interesting to examine possible hierarchical effects in multimodal stimulation or the effects of selective attention and relative stimulus salience on the interactions between sensory modalities. It is possible that the interaction effects between mismatch responses could index pre-conscious biasing mechanisms. Certain disorders show alterations in the aMMN, for example schizophrenia and dyslexia. This may result in alterations in the interactions between the senses. Along other lines, very little is known about the maturational changes underlying the sMMR and nothing about how the interactions between the different sensory modalities changes through development. One final avenue of exploration is the characterization of the MP1 component. It appears to be unique to the somatosensory system and have a separate generator to the MN1 component. Very little is known about the characteristics of this component, where it is

generated or what underlying process it reflects. The results of experimentation often lead to more questions than they answer and this thesis has proven to be no exception.

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Appendix 1 – Ethics application form

THE GOS/ICH RESEARCH ETHICS COMMITTEE

APPLICATION FORM

Appendix 2 – Consent form

REC No. 02NR10 Version 1, dated 25/06/2002

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARTICIPANTS in Research Studies

Title: Somatosensory event related potentials as a reflection of haptic memory processing

NOTES FOR PARTICIPANTS

1. You have been asked to take part in some research. The person organising that study must explain the project to you before you agree to take part.

2. Please ask the researcher any questions you like about this project, before you decide whether to join in.

3. If you decide, now or at any other time, that you do not wish to be involved in the research project, just tell us and we will stop the research. If you are a patient your treatment will carry on as normal.

4. You will be given an information sheet which describes the research. This information is for you to keep and refer to at any time. *Please read it carefully.*

5. If you have any complaints about the research project, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, or if urgent, by telephone and the committee administration will put you in contact with him.

CONSENT

I _____ agree that the Research Project named above has been explained to me to my satisfaction, and I agree to take part in this study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

SIGNED	PRINTED	DATE
_____	_____	_____
SIGNED (Researcher)	**PRINTED**	**DATE**
_____	_____	_____

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARENTS OR GUARDIANS of Children Participating in Research Studies

Title: Somatosensory event related potentials as a reflection of haptic memory processing

NOTES FOR PARENTS OR GUARDIANS

1. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

2. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

3. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice any present or future treatment.

4. You will be given an information sheet which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***

5. If you have any complaints about the way in which this research project has been or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I/We _____, being the parent(s)/guardian(s) of _____ agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

SIGNED (Parent (s)/Guardian (s))	**PRINTED**	**DATE**
_____	_____	_____
SIGNED (Researcher)	**PRINTED**	**DATE**
_____	_____	_____

Appendix 3 – Subject information sheet

SUBJECT INFORMATION

SOMATOSENSORY EVENT RELATED POTENTIALS AS A REFLECTION OF HAPTIC MEMORY PROCESSING

The aim of the study

The aim of this study is to examine one possible mechanism of tactile memory. The electrical response of the cerebral cortex to an ongoing, unchanging vibrating stimulus is recorded and then we determine how this response alters when the vibration is briefly changed. Changes in the cortical response may reflect the process in which the brain remembers the unchanging vibration stimulus and realizes the new stimulus is different.

Why is the study being done?

In some patients damage occurs to the somatosensory (touch sensitive) parts of the brain and these patients can be left with a number disabilities including difficulties in recognizing objects or texture changes through touch. We hope that this study will help to characterize one of the processes involved in touch memory.

How is the study to be done?

Should you decide to participate in this study, you/your child will undergo an EEG (electroencephalogram) while a vibration stimulus will be applied to the first and second fingers of one or both hands individually. This test will occur in the Clinical Neurophysiology Department, Great Ormond Street Hospital for Sick Children.

The EEG will be done by the researcher and involves placing a set of 62 electrodes (small metal disks attached to a wire) on the surface of the scalp. The scalp is lightly cleaned with an exfoliating agent and the electrodes are held in place with an electro-conductive paste and/or a small plaster. The paste is water soluble and will wash out following the procedure. In smaller children a net hat will be placed over top of the electrodes to help keep them in place. The hand will then be placed in a rest with the fingers against a small bar which will vibrate. You may be asked to watch a video during the test and to disregard the stimulus or you may be asked to count the number of times the stimulus changes during the test.

What are the risks and discomforts?

There are no anticipated risks to this project. Some younger patients object to the electrode placement but tend to quickly settle once they are in place. Nothing can be felt from the scalp electrodes and they do nothing but record the ongoing electrical activity of the brain in a manner similar to those used to record heart beats in the ECG . The vibration stimulus is not painful, but is a somewhat odd sensation that some people find uncomfortable when experienced over a prolonged period of time.

What are the potential benefits?

This study will not bring any immediate benefits to the participants. However, it is hoped that this will further our understanding of memory processing in the brain and this information will aid in diagnosing problems in this area.

Who will have access to the case/research records?

Only the researchers and a representative of the Research Ethics Committee will have access to the data collected during this study.

The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact the Data Protection Officer via the switch board on extension .

Do I have to take part in this study?

No. If you decide, now or at a later stage, that you do not wish to participate in this research project, that is your right and will not in any way prejudice any present or future treatment.

Who do I speak to if problems arise?

Please contact Ms. Lynne Spackman or Dr. Stewart Boyd directly if there are any problems relating to this study.

If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethic Committee, by post via the Research and Development Office, Institute of Child Health, or if urgent, by telephone on and the Committee administration will put you in contact with him.

Details of how to contact the researcher:

Lynne Spackman: *tel*: or *e-mail*:

Appendix 4 – Trigger vs. Stimulus output latencies

Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)	Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)
1	186	206	20	21	194	220	26
2	188	206	18	22	194	212	18
3	188	204	16	23	194	210	16
4	188	206	16	24	194	212	18
5	188	214	26	25	194	212	18
6	188	214	26	26	196	218	22
7	188	214	26	27	196	218	22
8	190	212	22	28	196	220	24
9	190	214	24	29	196	218	22
10	190	214	24	30	196	214	18
11	190	212	22	31	196	218	22
12	190	214	24	32	198	220	22
13	192	214	22	33	198	220	22
14	192	204	12	34	198	220	22
15	192	212	20	35	200	218	18
16	192	212	22	36	200	218	18
17	192	214	22	37	200	218	18
18	192	214	22	38	200	218	18
19	192	212	20	39	202	216	14
20	192	214	22	40	202	218	16

Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)	Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)
1	84	110	26	21	288	310	22
2	286	310	24	22	88	108	20
3	86	110	24	23	90	108	18
4	286	310	24	24	290	308	18
5	86	110	24	25	90	110	20
6	286	308	22	26	290	316	26
7	86	110	24	27	90	108	18
8	288	310	22	28	290	308	18
9	88	110	22	29	90	108	18
10	288	310	22	30	290	308	18
11	86	108	22	31	94	112	18
12	288	310	22	32	296	310	14
13	88	108	20	33	98	112	14
14	288	308	20	34	298	312	14
15	88	110	22	35	298	322	24
16	288	310	22	36	98	122	24
17	88	110	22	37	300	322	22
18	288	310	22	38	100	122	22
19	88	108	20	39	100	122	22
20	88	116	28	40	300	322	22

Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)	Number	Trig Output (ms)	Stim Output (ms)	Difference (ms)
1	192	206	14	21	194	208	14
2	192	208	16	22	194	210	16
3	194	208	14	23	194	208	14
4	192	206	14	24	194	210	16
5	192	208	16	25	194	210	16
6	192	208	16	26	194	210	16
7	192	208	16	27	194	210	16
8	192	208	16	28	194	208	14
9	192	206	14	29	194	208	14
10	192	206	14	30	194	210	16
11	192	208	16	31	194	212	18
12	192	210	18	32	194	210	16
13	192	210	18	33	194	210	16
14	192	210	18	34	194	210	16
15	194	210	16	35	196	210	14
16	194	208	14	36	196	210	14
17	194	208	14	37	194	208	14
18	194	208	14	38	194	208	14
19	194	208	14	39	194	208	14
20	194	208	14	40	192	206	14

Appendix 5 – Edinburgh Handedness Inventory

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities by putting a check in the appropriate column. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, put 2 checks. If in any case you are really indifferent put and a check in both columns.

Some of the activities listed below require the use of both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

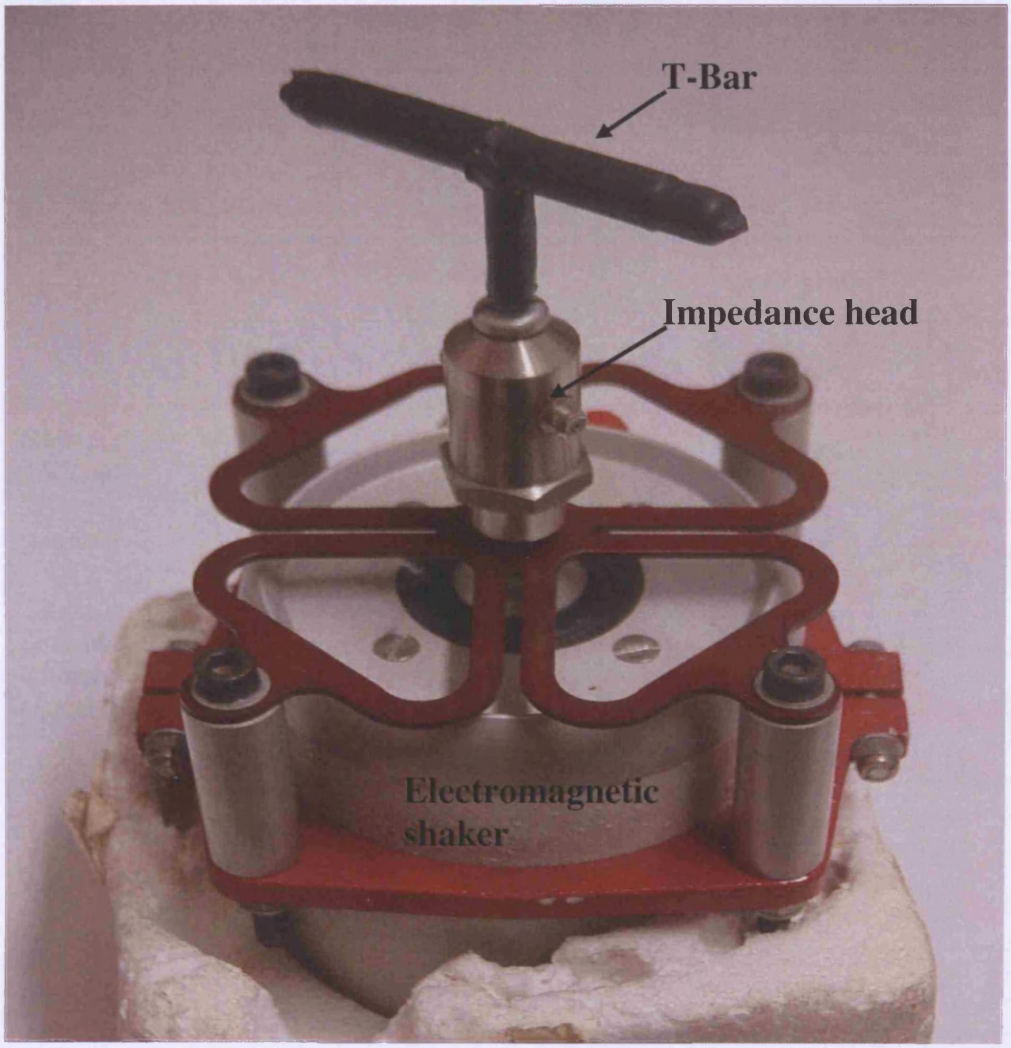
Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	⌐ ⌐	⌐ ⌐
2. Drawing	⌐ ⌐	⌐ ⌐
3. Throwing	⌐ ⌐	⌐ ⌐
4. Scissors	⌐ ⌐	⌐ ⌐
5. Toothbrush	⌐ ⌐	⌐ ⌐
6. Knife (without fork)	⌐ ⌐	⌐ ⌐
7. Spoon	⌐ ⌐	⌐ ⌐
8. Broom (upper hand)	⌐ ⌐	⌐ ⌐
9. Striking Match (match)	⌐ ⌐	⌐ ⌐
10. Opening box (lid)	⌐ ⌐	⌐ ⌐
TOTAL(count X's in both columns)	⌐	⌐

Scoring:
Add up the checks in both left and right columns.
Whichever number is greater, would be considered your handedness.

(Oldfield, R.C. (1971) The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*, 9: 97-113.)

Appendix 6 – Vibrotactile stimulator



Electromagnetic shaker, impedance head with force transducer and T-bar used to produce the vibrotactile stimuli for all experiments performed in this thesis.

Appendix 7 – Results of experiments 6 & 7

Stim			Lat (ms)	Amp (μV)	Stim			Lat (ms)	Amp (μV)
20ms deviant/ 70ms standard	RH	MN1	124.6 ±11.6	1.11 ±0.59	70ms deviant/ 20ms standard	RH	MN1	126.2 ±13.1	1.10 ±0.33
	RH	MP1	-	-		RH	MP1	188.2 ±24.5	0.86 ±0.50
	LH	MN1	125.4 ±11.2	0.93 ±0.42		LH	MN1	125.5 ±15.7	0.77 ±0.37
	LH	MP1	-	-		LH	MP1	193.7 ±26.8	0.91 ±0.71
50ms deviant/ 150ms standard	RH	MN1	140.7 ±14.8	1.14 ±0.50	150ms deviant/ 50ms standard	RH	MN1	140.9 ±12.9	0.92 ±0.38
		MP1	-	-			MP1	221.8 ±27.2	0.95 ±0.57
170ms deviant/ 250ms standard*	RH	MN1	205.8 ±24.7	1.36 ±0.74	250ms deviant/ 170ms standard*	RH	MN1	209.4 ±33.0	1.08 ±0.40
		MP1	-	-			MP1	-	-
70Hz deviant/ 200Hz standard	RH	MN1	125.4 ±15.5	1.13 ±0.34	200Hz deviant/ 70Hz standard	RH	MN1	129.4 ±14.3	0.91 ±0.51
	RH	MP1	196.5 ±28.8	1.10 ±0.59		RH	MP1	202.2 ±24.1	0.99 ±0.55
	LH	MN1	129.8 ±12.0	0.87 ±0.36		LH	MN1	128.4 ±11.3	1.01 ±0.55
	LH	MP1	195.4 ±30.9	1.07 ±0.57		LH	MP1	193.2 ±17.7	0.99 ±0.44

Table 1: Average peak latency and amplitude measurements for the MN1 and MP1 subtraction waveform components at Cz for each of the stimulus conditions used. * n = 5.

RH – Right hand

LH – Left hand

Stimulus Pairs	Incorrect response		Correct response	
	Frequency	Percentage	Frequency	Percentage
20_70ms	14	15.6	76	84.4
70_20ms	9	10.0	81	90.0
50_150ms	20	22.2	70	77.8
150_50ms	7	7.8	83	92.2
170_250ms	73	81.1	17	18.9
250_170ms	70	77.8	20	22.2
20_20ms	10	11.1	80	88.9
50_50ms	7	7.8	83	92.2
70_70ms	9	10.0	81	90.0
150_150ms	9	10.0	81	90.0
170_170ms	2	2.2	88	97.8
250_250ms	6	6.7	84	93.3
70_200Hz	9	10.0	81	90.0
200_70Hz	15	16.7	75	83.3
70_70Hz	4	4.4	86	95.6
200_200Hz	7	7.8	83	92.2

Table 2: Results of the discrimination experiment. Subjects participating in experiments 1 and 2 were asked to perform a task in which they had to discriminate between two pairs of stimuli similar to those used in the experiments. There was a tendency to make more errors in discrimination if the shorter duration stimulus was presented first. This was significant ($p<0.05$) between 150ms and 50ms paired stimuli.

Appendix 8 – Publications and presentations

Papers:

Spackman, L., Boyd, S., Towell, A. (2007). Effects of stimulus frequency and duration on somatosensory discrimination responses. Experimental Brain Research, 177, 21-30.

Spackman, L., Boyd, S., Towell, A. (2006). Identification and characterisation of somatosensory off responses. Brain Research, 1114, 53-62

Platform presentations with published abstracts:

L.A. Spackman, S.G. Boyd, A. Towell (2006) Characterization of somatosensory discrimination responses using scalp and intracranial recordings. *Clinical Neurophysiology*, 117(S1), 1.

Spackman, L., Boyd, S., Towell, A. (2006) Characterization of somatosensory discrimination responses using scalp and intracranial recordings. Abstracts of the 28th International Congress of Clinical Neurophysiology. Clinical Neurophysiology, 117 (Suppl. 1), S100.